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Restoration of middle-ear input in fluid-filled middle ears by controlled introduction of air or a novel air-filled implant

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Abstract

The effect of small amounts of air on sound-induced umbo velocity in an otherwise saline-filled middle ear (ME) was investigated to examine the efficacy of a novel balloon-like air-filled ME implant suitable for patients with chronically non-aerated MEs. In this study, air bubbles or air-filled implants were introduced into saline-filled human cadaveric MEs. Umbo velocity, a convenient measure of ME response, served as an indicator of hearing sensitivity. Filling the ME with saline reduced umbo velocity by 25–30 dB at low frequencies and more at high frequencies, consistent with earlier work (Ravicz et al., Hear. Res. 195: 103–130 (2004)). Small amounts of air (~30 μ l) in the otherwise saline-filled ME increased umbo velocity substantially, to levels only 10–15 dB lower than in the dry ME, in a frequency- and location-dependent manner: air in contact with the tympanic membrane (TM) increased umbo velocity at all frequencies, while air located away from the TM increased umbo velocity only below about 500 Hz. The air-filled implant also affected umbo velocity in a manner similar to an air bubble of equivalent compliance. Inserting additional implants into the ME had the same effect as increasing air volume. These results suggest these middle-ear implants would significantly reduce conductive hearing loss in patients with chronically fluid-filled MEs.

Graphical abstract

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Keywords

Middle ear; otitis media; effusion; implant; aeration

1. Introduction

Middle-ear effusion (fluid in the middle ear) is a well-known cause of conductive hearing loss, and otitis media with effusion (OME) is responsible for thousands of medical office visits each year (Lieberthal et al., 2013) and affects millions worldwide (Merchant et al., 1998b; Monasta et al., 2012). The effusion can be serous or mucoid (e.g., Cunningham and Eavey, 1993) and can be the result of middle-ear disease or other conditions that result in poor middle-ear (ME) aeration. The presence of ME effusion (and any associated ME static pressure) induces a conductive hearing loss of generally 20–40 dB in cases of acute OME (Bluestone et al., 1973; Fria, 1985; Merchant and Rosowski, 2003) and up to 60–70 dB in cases of chronic otitis media (COM; Merchant et al., 1998b; Merchant and Rosowski, 2013).

In cases of acute OME, the hearing loss is usually resolved when the fluid is drained to aerate the ME via myringotomy and placement of a tympanostomy tube (e.g., Bluestone and Klein, 2007). The myringotomy also relieves any static pressure difference across the tympanic membrane (TM) and improves the quality of life (Witsell et al., 2005). While conditions leading to OME often abate after normal clinical and surgical treatment, in a significant fraction of cases the effusion returns when the myringotomy is healed, and the conductive hearing loss recurs (Cassebrandt et al., 1992; Nadol and McKenna, 2005; Gaihede et al., 2007; Gulya et al., 2010; Lieberthal et al., 2013) – perhaps due to the same dysfunction in ME aeration that led to the effusion in the first place.

With COM, the standard therapy is surgical (mastoidectomy and tympanoplasty procedures), with the goals of surgery being eradication of disease, prevention of recurrence, and improvement in hearing. In the United States, over 70,000 tympanoplasty surgeries are performed annually (Ruben, 1982). While tympanomastoid surgery is successful in controlling infection with a success rate in excess of 80–90%, postoperative hearing results are more modest (Nadol and McKenna, 2005; Gulya et al., 2010): In general, long-term closure of the air-bone gap to 20 dB or less occurs in only 40–70% of cases (Merchant et al., 1998a, 1998b). The most common cause of failure of tympanoplasty to restore hearing is non-aeration of the ME due to chronic Eustachian tube dysfunction or deposition of fibrous tissue (Merchant et al., 1998a). Though balloon dilation tuboplasty has shown promise as a way to improve ME aeration by enlarging the Eustachian tube orifice (e.g., Ockermann et al., 2010; Poe et al., 2011), the long-term outcome of this procedure is still under examination. Thus, currently there is no approved long-lasting and reliable way of re-aerating the MEs of patients with COM after tympanomastoidectomy surgery.

In an earlier study of mechanisms of hearing loss in OME (Ravicz et al., 2004), in which saline or silicone fluid was instilled into cadaver MEs through the Eustachian tube to mimic ME effusion, we showed that (a) reductions in sound-induced umbo velocity due to ME fluid match hearing loss in OME patients (when the effect of ME static pressure is taken into account) and (b) the reduction in umbo velocity with fluid present is produced by different

mechanisms in different frequency ranges. At low frequencies (500 Hz and below), the reduction in umbo velocity is independent of the location of the fluid, and the primary effect of the fluid is consistent with a reduction in ME compliance (the ability of the TM to move in response to sound) caused by the replacement of the compressible air in the ME with incompressible fluid (Fig. 1A). A simple model predicted the reduction in umbo velocity fairly well (Fig. 1A). At high frequencies (above 1–2 kHz), the reduction is due to an increase in the effective mass of the TM by the fluid contacting it, and the same amount of fluid produces a greater reduction if it is contact with the TM than if it is in other parts of the ME remote from the TM (Fig. 1B). Completely filling the ME air spaces with fluid, which proved to be difficult to achieve, resulted in 25–35 dB reductions in TM and umbo motion across all tested frequencies. A conclusion from that study is that a small amount of air in the otherwise fluid-filled ME partly lessens the reduction in umbo velocity (Fig. 1C) and should restore some hearing. Similar conclusions were reached in live animal studies (Guan and Gan, 2013; Guan et al., 2014).

There are also clinical demonstrations that the presence of small amounts of air or other gases in the otherwise effusion-filled ME improve hearing sensitivity (e.g., Andréasson et al., 1978, 1983; Koch and Becker, 1981). To this end, some clinicians and investigators have injected air or gases with lower diffusivity into the effusion-filled MEs of patients (e.g., Koch and Becker, 1981; Andréasson et al., 1983; Silverstein et al., 1993; Silman et al., 2005). These injections produce transitory improvements in hearing that are eventually reduced to the original pathological state. The limiting factor in this transitory improvement is the time required for the air or other gas to be absorbed and replaced by fluid (Andréasson et al., 1983) – generally on the order of a few days to a few weeks.

This success in restoring hearing in fluid-filled MEs, even on a transitory basis, points out that a balloon-like implant that maintains a small air volume in the ME could provide a longer-term solution for hearing loss in chronic OME. A successful implant that provides a permanent functional air space must satisfy the following conditions (Merchant et al., 2010): (1) *Physical properties*: It must be sufficiently small to fit into the ME without hindering the motion of the ossicles or other ME structures important for hearing. (2) *Barrier properties*: It must resist diffusion of air and exudate to maintain an air-filled space in a physiological environment. (3) *Acoustical properties*: It must have sufficient acoustic compliance to allow sound waves to compress it. (4) *Biocompatibility properties*: It must resist degradation from physiological processes inside the body and must not invoke a physiological foreign-body response. Previous attempts to develop such an implant (e.g., Gaudin, 1968; Gerhardt, 1984) have failed because they have been unable to meet these conditions.

In this paper we evaluate (1) the effects of the presence and location of a small air bubble in a saline-filled ME on sound-induced umbo motion, and (2) the performance of a novel ME implant that satisfies the conditions described above. To perform this evaluation we use the temporal-bone preparation developed for our investigations of the effect of fluid on ME sound conduction (Ravicz et al. 2004). Such cadaveric temporal bone preparations have been shown to be representative of the live ear for many ME processes (e.g., Rosowski et al., 1990; Goode et al., 1993; Rosowski et al., 2007; Chien et al., 2009) and have been used to study the effects of ME fluid on hearing (Ravicz et al., 2004; Gan et al., 2006; Dai et al.,

2008; Zhang et al., 2014). In this paper we further explore the effects of small air bubbles in a saline-filled cadaveric ME and determine the effects of total air volume and location on umbo velocity. We introduce one or more implants into an otherwise saline-filled ME and demonstrate that the effect of the implants on umbo velocity are comparable to that of air bubbles of similar compliance and location within the ME. These novel ME implants could restore hearing in patients with chronically non-aerated MEs.

2. Materials and Methods

2.1. Preparation

The management of human data was performed in accordance with guidelines published by the U.S. Public Health Service for the use of de-identified post-mortem human material.

Four temporal bones (28B, 31R, 32R, 33R) were prepared as described previously (Ravicz et al., 2004; Chien et al., 2006). One of the bones (28B) was also used in the Ravicz et al. (2004) experiments, and two of the bones (28B, 32R) were used in experiments on multiple days. Briefly, the temporal bones (ages 67 to 75 years with a mean of 69 years) were carefully removed at autopsy (to avoid damaging the dura covering the endolymphatic sac) and examined for normality by visual inspection of the ear canal, TM, ME, and mastoid and by chart review for absence of otologic disease. As shown in Fig. 2A, the cartilaginous ear canal was removed, and a brass sealing ring 14 mm outer diameter, 5 mm inner diameter and 2 mm thick was centered over the lateral end of the bony ear canal and fixed in place with dental cement (Durelon, ESPE, Seefeld, Germany). A small (1.5 mm dia.) opening was made in the inferior ear canal wall. In one ear (28B), a metal sleeve (18 gauge hypodermic tubing, 1.25 mm outer diameter, 0.8 mm inner diameter, 13 mm length) was cemented in place to allow a probe-tube microphone to be positioned within 4–10 mm of the umbo. Another opening (3 mm diameter) was made in the anterior canal wall to provide a view of the umbo of the malleus perpendicular to the plane of the tympanic ring. The mastoid air cells were removed by drilling from a lateral approach while keeping the posterior canal wall, inner ear, and tegmen tympani intact.

The facial recess was opened and the mastoid segment of the facial nerve was removed to permit access to the ME for introduction of saline or implants and other manipulations. Small round or oval brass rings (5–8 × 8–12 mm dia., 2 mm thick) were cemented on the posterior surface of the facial recess opening and just posterior to the aditus ad antrum to allow these openings to be sealed easily with transparent windows. The stapedius tendon was cut. The soft tissue in the mandibular fossa and carotid canal was removed. The cartilaginous portion of the Eustachian tube was removed, the bony Eustachian tube was enlarged slightly, and a metal sleeve (similar to the one through the ear canal) was cemented into the tube to facilitate introducing saline or bubbles into the ME (Fig. 1). The remaining ME air volume in the preparation was measured as described in Section 2.3.2 below and was 800–1400 μ l in the four temporal bone specimens.

A short metal mounting post (6 mm dia.) was cemented to the inferior or posterior surface of the temporal bone, and all cut surfaces of the temporal bone (middle and posterior cranial fossae, petrous apex, mandibular fossa, jugular fossa and hypotympanum) where air cells

may communicate with the surroundings were covered with dental cement to prevent leakage of air into or fluid from the ME. Care was taken to avoid any physical trauma to the TM, ossicles, their suspensory ligaments, oval and round windows and the inner ear during the preparation procedure. The TM and ME were kept moist during preparation by periodic application (and subsequent removal) of normal (0.9%) saline to the exterior and interior surfaces.

2.2 Stimuli, instrumentation, responses, and metrics

Broadband chirp stimuli containing frequencies from 20 Hz to 20 kHz or from 24.4 Hz to 25 kHz were synthesized and responses were recorded using commercial (SysID, Richmond, CA) or custom software and hardware as described previously (Ravicz et al., 2004; Chien et al., 2006). Ear-canal sound pressure P_{EC} 2–5 mm from the TM was measured with a calibrated microphone and probe tube (ear 28B: Knowles EK-23207; others: Etymotic ER-7). Umbo velocity V_U (as evaluated by the velocity of a small 0.2 mm $\times$ 0.2 mm reflective tape target placed on the TM over the umbo) was measured with a laser-Doppler vibrometer (OFV-501 or HLV-1000, Polytec, Tustin, CA) with the laser beam focused on the target through the anterior ear-canal opening (Fig. 2A). V_U and P_{EC} spectra were computed from the average of 100–1000 stimulus presentations and saved to the computer.¹ In ear 28B, lower stimulus levels were used for P_{EC} measurements to avoid distortion in the P_{EC} microphone output (Ravicz et al., 2004). Post-processing was performed in Matlab (Mathworks, Natick MA).

2.3 Experimental technique

2.3.1 Middle ear dry and sealed—Measurements were made initially with the ME filled with air and sealed from the atmosphere (“normal” condition) as follows: The temporal bone was clamped by the mounting post to a vibration-isolated table and oriented approximately as it would be in a seated patient; this is the orientation during hearing tests, and this orientation also simplified removing air from the ME while it was being filled with saline (see below). Any saline used for moistening was suctioned from the ear, the microphone probe tube was inserted into the ear canal, and the sound pressure source was coupled to the brass ring in the ear canal and sealed with petrolatum. The vibrometer’s laser beam was aimed at the umbo target as described above. To seal the ear canal and ME from the atmosphere, the anterior ear canal, aditus, and facial recess openings were covered with small pieces of 2-mm thick acrylic sheet and sealed with petrolatum (Fig. 2A). No venting of the ear canal or ME was necessary: a small leak through the acoustic source prevented pressure buildup in the ear canal, and the covers for the ME openings were removed at roughly 10-minute intervals to perform manipulations as described below.

2.3.2 Saline and air in the middle ear—Saline was introduced into all or various parts of the ME, usually via the metal sleeve in the Eustachian tube: a calibrated syringe filled with normal saline (degassed in vacuum to encourage air trapped in the ME to dissolve into it) was attached to the sleeve with a polyethylene fill tube (Fig. 2A). As the saline was

¹Complex quantities (such as V_U) with real and imaginary parts are denoted by variables in bold type and are usually expressed as magnitude $|V_U|$ and phase-angle $\angle V_U$.

introduced slowly through the sleeve, it was monitored and manipulated as necessary with probes and light suction via the facial recess and antrum openings to minimize or manipulate trapped air. The later ears (31R, 32R, 33R) were subjected to moderate vacuum for 5–10 minutes while the ME was filled with saline and the ear was immersed in saline to encourage trapped air to escape or to dissolve into the saline when the ear was removed from vacuum. This procedure was partially successful, as we were able to obtain reductions in V_U comparable to the “best” example in the previous study (28B, Ravicz et al., 2004; see Fig. 3C below), but the reductions were less than the 40 dB hearing losses observed in OME ears (e.g., Merchant and Rosowski, 2003). The windows were then installed over the ME openings to seal the ME from the atmosphere as described above, and the ME was inspected through the transparent windows to check that no unwanted air was trapped in that portion of the ME visible through the windows. Total ME volume was estimated by measuring the quantity of saline necessary to fill the ME from the calibrated syringe, and the residual ME air volume V_{MEC} when the ME was partly filled with saline was computed by subtracting the amount of saline introduced into the ME from the total ME volume. Saline (kinematic viscosity 1 centistoke (cSt); dynamic viscosity = 1 centipoise (cP)) was used to simulate serous effusions common with OME.

2.3.3. Bubbles and implants—Umbo velocity was measured after air bubbles were introduced into various parts of the saline-filled ME through the fill tube in the Eustachian tube or under one of the window covers (Fig. 2A) using a calibrated syringe. In this manner, the bubble volume and location could be controlled fairly closely; volume uncertainty was $\pm 20\%$. Bubbles not in contact with the TM were generally in the attic or in contact with one or both of the window covers. Bubbles in contact with the TM were generally in contact with the inferior part of the TM (though we did not take note during the experiment of the specific location of individual bubbles), as the anatomy of the ME cavity could be used to hold them in place.

The ME implant comprises an air volume of 16–30 microliters (μl) enclosed by a thin plastic film to form a balloon-like structure (see Fig. 2B, 2C). A final version of the implant, which met the conditions outlined in the Introduction, was used in ears 31R, 32R, and 33R; a preliminary version, which provided a proof of concept and had the necessary physical and acoustical properties but did not meet the barrier and biocompatibility conditions, was used in ear 28B.

For evaluating implant performance, the important metric is the equivalent acoustical volume (EAV), defined as the volume of air that has the same acoustical compliance as the implant. The EAV is always smaller than the actual volume because it includes the stiffness of the implant wall, which tends to reduce the total compliance. The implants used in these experiments had an acoustical volume that was 50–85% of their actual volume. The methods for determining actual and acoustical implant volumes are described in the Appendix. The uncertainty in EAV was about 15%.

The implants were inserted into the ME through one of the windows, and the window covers were replaced. In some cases, the syringe was used to introduce a small flow of saline into the ME while the cover was open to keep air from entering the ME. For some

measurements, one or more implants were inserted into the mesotympanum so they contacted the TM; for others, the implants were inserted through the facial recess window into the enlarged facial recess or into the pro-, meso-, or hypotympanum relatively remote from the TM (Fig. 2B). As described above for bubbles, though we did not note the specific locations of individual implants in contact with the TM, these implants generally contacted the inferior part of the TM.

2.4 Checks of ears and experimental conditions

Before experiments, the ears were visually checked for normality. $\mathbf{V_U}$ was measured with the ME dry and sealed before the saline-filling part of the experiments and periodically during experiments. $\mathbf{V_U}$ in this “normal” condition in the four ears, normalized by $\mathbf{P_{EC}}$, is shown in Fig. 3A, truncated at 4–8 kHz as described below. Normalized $\mathbf{V_U}$ magnitude varied by a factor of 2–3 among the four ears below 1 kHz and above 2.5 kHz; normalized $\mathbf{V_U}$ phase is quite similar among the four ears. Variations in $|\mathbf{V_U}|$ between repeated measurements were less than 15% (1.5 dB). The mean $\mathbf{V_U}$ in the four ears is shown by the thick black line. The range of the normalized $\mathbf{V_U}$ (gray shading) is similar to normalized umbo velocity from other studies (Fig. 3B) using fresh or thawed temporal bones with the ME intact or open (Ravicz et al., 2004; Nakajima et al., 2005; Gan et al., 2006; Dai et al., 2008; Homma et al., 2010; Zhang et al., 2014) or in live human subjects (Rosowski et al., 2012).

Though the measured $\mathbf{V_U}$ was greater than the whole-bone motion and the instrumentation noise floor up to 10–15 kHz, the high-frequency accuracy of normalized $\mathbf{V_U}$ was limited by the frequency range over which the measured $\mathbf{P_{EC}}$ is a good estimate of the sound pressure at the umbo (which we have assumed is representative of the umbo input). At high frequencies, generally where the distance between the $\mathbf{P_{EC}}$ probe tube tip and the umbo exceeds 1/8 sound wavelength, $\mathbf{P_{EC}}$ and umbo sound pressure can differ substantially (e.g., Ravicz et al., 2004). For this reason, we omit normalized $\mathbf{V_U}$ data above 4–5 kHz. Because $\mathbf{P_{EC}}$ is invariant whether the ME contains saline or is dry, we can present ratios of $\mathbf{V_U}$ in different conditions to higher frequencies, up to 10 kHz.

We showed previously (Ravicz et al., 2004, Sec. 4.4.3) that any air in the inner ear could provide additional compliance to facilitate umbo motion in a fluid-filled ME. In ears 31R, 32R, and 33R, we verified that no air had entered the inner ear by also measuring round-window velocity to check that the phase difference between stapes and round-window motion below 1 kHz was approximately one-half cycle (e.g., Mehta et al., 2003)².

To evaluate the efficacy of our procedures to replace all air in the ME with saline, we computed the change in $\mathbf{V_U}$ ($\Delta \mathbf{V_U}$) from the normal condition.³ As we demonstrated

²Because the intact cochlea is approximately incompressible, and the oval and round windows form the only flexible portions of the cochlear wall (Merchant et al., 1996, 1997), volume velocity of the stapes at low frequencies should be accompanied by equal and opposite volume velocity of the round window. A different result indicates that a mobile “third window” or a compressible element has entered the cochlea (e.g., Shera and Zweig, 1992; Merchant and Rosowski, 2008). In the case of temporal bone experiments, the usual cause is an air bubble in the cochlea.

³Note that this definition of $\Delta \mathbf{V_U}$ is the opposite of that in Ravicz et al. (2004), where $\mathbf{V_U}$ was defined as the *reduction* in $|\mathbf{V_U}|$ when the state of the ME was changed from its normal condition. This definition results in a change in the sign of $\Delta \mathbf{V_U}$ between the two studies.

previously (Ravicz et al., 2004), a large fluid-induced reduction in low-frequency $|V_U|$ ($|V_U| < -25$ dB) indicates that all or nearly all air was removed from the ME and the specimen represents a clinically fluid-filled ME, while a low-frequency reduction in $|V_U|$ of less than 20 dB suggests that a significant volume of air remained trapped somewhere in the ME. For the experiments described in this paper, it was important that as much air be removed as possible so as not to obscure the effects of the introduction of small amounts of air or implants in the ME. Typical $|V_U|$ before and after experiments with air bubbles or implants are shown in Fig. 3C. In two ears (28B and 32R), we were able to achieve a $|V_U|$ reduction of nearly 30 dB, close to the 40-dB hearing loss commonly seen clinically in cases of OME. We achieved this 30-dB $|V_U|$ reduction on two different days in these ears. In two other ears (31R, 33R), we were able to achieve a maximum $|V_U|$ reduction of 15–20 dB, which was sufficient to show effects at 250 Hz and above.

As we have argued previously (Ravicz et al., 2004), it is reasonable to use data from the ears with the greatest $|V_U|$ reduction as the best estimates of results in real ears.

3. Results

3.1. Effect of air bubbles in a saline-filled middle ear

As an example, Fig. 4A shows $|V_U|$ in ear 32R with the ME filled with saline and with small bubbles of various sizes in the saline-filled ME. For simplicity, we begin with an example in which the bubble was in the facial recess where it was not in contact with the TM.

Consistent with our conclusions in Ravicz et al. (2004, Figs. 7 and 11(a)), filling the ME with saline reduces $|V_U|$ substantially at all frequencies ($|V_U|$ is about -25 dB), and the presence of air in the ME facilitates an increase in $|V_U|$ when the ME is otherwise filled with fluid. In Fig. 4A, the bubbles were not in contact with the TM, and the increase is only at low frequencies. The roughly 0.3-cycle reduction in $\angle V_U$ with a bubble, in the frequency band between the $|V_U|$ peak near 0.4 kHz and the $|V_U|$ notch near 0.8 kHz ($\angle V_U$ is about -0.3 cycles), is consistent with a resonance-antiresonance pair due to the interaction of the compliance of the bubble and TM and the mass of the ME saline. The shift of the $|V_U|$ peak to lower frequencies as bubble size (and therefore bubble compliance) increases is consistent with this view. Note that, at the frequency of the antiresonance ($|V_U|$ notch and $+0.3$ -cycle $\angle V_U$ step), $|V_U|$ with a bubble is actually *lower* than with no bubble present. Additional antiresonances involving a portion of the ME saline mass may explain the lower $|V_U|$ and lower $\angle V_U$ between 0.8 and 2 kHz. Larger bubbles facilitate a greater low-frequency $|V_U|$ increase than smaller bubbles.

The effect of an air bubble of comparable size in contact with the TM in the same saline-filled ME is shown in Fig. 4B. Also shown is the curve for a 20- μ l bubble not on the TM, from Fig. 4A. At low frequencies, the effect of the bubble is fairly independent of whether it is in contact with the TM or not, consistent with Fig. 11(a) of Ravicz et al. 2004 (see Fig. 1A). It can be seen, however, that the frequencies of the $|V_U|$ peaks and notches and $\angle V_U$ steps are slightly higher than in Fig. 4A, perhaps because the bubble is not surrounded by saline and the effective fluid mass is lower. At high frequencies, the effect of the bubble varies with its location: A bubble contacting the TM produces a much greater increase in $|V_U|$ than a bubble that does not contact the TM.

Similar results were obtained in the other two ears in which the effect of air bubbles was measured. Figure 5 summarizes the effect of bubble size and location on $|\mathbf{V}_U|$ in these three saline-filled MEs (28B, 32R, 33R) at two representative frequencies: (a) a low frequency, 250 Hz; and (b) a high frequency, 2 kHz. In general, effects were more variable at intermediate frequencies, and effects at 2 kHz were similar to effects at higher frequencies (see Fig. 4). In both panels, $|\mathbf{V}_U|$ measured in the three ears when they were filled with saline are shown by the triangles on the left-hand axis, $|\mathbf{V}_U|$ with bubbles in contact with the TM (generally on the inferior part; see Sec. 2.3.3) are shown with open symbols, and $|\mathbf{V}_U|$ with bubbles not in contact with the TM are shown with filled symbols. At low frequencies (Fig. 5A), $|\mathbf{V}_U|$ generally increased as bubble size increased, regardless of the location of the bubble. At high frequencies (Fig. 5B), the reduction in $|\mathbf{V}_U|$ with ME saline was generally 10 – 20 dB less with bubbles in contact with the TM than with bubbles not in contact.

The low-frequency increase in $|\mathbf{V}_U|$ in a saline-filled ME with an increase in bubble size, independent of bubble location, is consistent with the results and the model prediction presented in Ravicz et al. (2004) (see also Figs. 1A, 1C, and 4A, solid line). The smaller high-frequency $|\mathbf{V}_U|$ reduction by saline when the bubble was in contact with the TM is also consistent with the Ravicz et al. (2004) results (see also Fig. 1B).

As discussed in the Methods, with saline in the ME we were able to achieve a low-frequency reduction in $|\mathbf{V}_U|$ of 20–30 dB in these three ears (left triangles in Fig. 5A), considerably less than what would be predicted by the compressibility of saline and less than the 40-dB hearing loss seen clinically in cases of OME. As discussed in Ravicz et al. (2004), a residual ME compliance, probably due to air trapped somewhere in our preparation out of view from the windows, facilitates measureable umbo velocity even in a nominally fluid-filled ME. Fig. 5A includes $|\mathbf{V}_U|$ predicted from a modified model (dashed line) that includes a residual (shunt) compliance, based on the circuit in Fig. 15 of Ravicz et al. (2004). The value of the residual compliance is determined from the smallest $|\mathbf{V}_U|$ we observed and is equivalent to a 13- μl air bubble. This modified model provides a better prediction of our measured low-frequency $|\mathbf{V}_U|$ with air bubbles of various sizes in the saline-filled ME.

3.2. Equivalency of implants and air bubbles

We demonstrate the efficacy of the implant in restoring ME input in a fluid-filled ME by comparing the effects of implants on $|\mathbf{V}_U|$ to the effect of ME bubbles. To aid evaluation, we compare $|\mathbf{V}_U|$ with two implants to $|\mathbf{V}_U|$ with a bubble in the same location as the implants and of a size approximately equal to the implants' equivalent acoustical volume (see Sec. 2.3.3).

Because the maximum increase in umbo velocity in a fluid-filled ME over the widest frequency range is of greatest clinical importance, we first show a case where the implant or bubble is in contact with the TM. For example, Fig. 6A shows that $|\mathbf{V}_U|$ in saline-filled ear 32R with two implants (with a total equivalent air volume of 26 μl) on the TM (green dashed curve) is nearly identical to $|\mathbf{V}_U|$ with an air bubble of volume $\approx 20 \mu\text{l}$ (red dot-dashed curve): At low frequencies, either the bubble or the implant increased $|\mathbf{V}_U|$ from about –25

dB to about -17 dB. Interestingly, V_U with two implants does not have the $|V_U|$ notch and negative $\angle V_U$ step seen in V_U with the bubble. Similarly, the change in V_U facilitated by two implants not in contact with the TM is similar at most frequencies to the change in V_U facilitated by a $\sim 20\text{-}\mu\text{l}$ bubble not in contact with the TM (Fig. 6B). In this case, V_U with implants shows similar $|V_U|$ notches and negative $\angle V_U$ steps to V_U with a bubble (see also Fig. 4A). Fig. 6 demonstrates that a pair of implants acts acoustically as an air bubble of volume equal to the total *EAV* of the implants.

3.3. Consistency in implant measurements, properties, and placement

For the implant to be useful clinically, it is important that its properties be uniform between samples and that it can be repeatably and reliably placed within the ME. Fig. 7 shows V_U for six different implants placed individually in the same ME location in contact with the TM in the saline-filled ME of ear 32R. V_U was quite similar among the six implants, especially at low frequencies: At 250 Hz, the V_U s.d. among the implants is less than 1 dB ($\sim 12\%$); at 2 kHz and above, the s.d. is about 2 dB ($\sim 25\%$). The s.d. is slightly higher between 0.5 and 1.6 kHz, consistent with the observation of greater variability among V_U with air bubbles in this frequency range described in Fig. 5. The s.d. in V_U among implants is comparable to the variation in absolute volume among the implants ($14\% \approx 1.1$ dB) and to the variability in measurements of repeated placement of the same implant (~ 2 dB).

3.4. Effect of location: 1 implant

As can be seen in Fig. 6 above, whether an implant is in contact with the TM or not has little effect at low frequencies but a substantial effect at higher frequencies. This location effect is shown more directly in Fig. 8, which shows V_U in ear 32R with the ME filled with saline and with the same implant in three different locations within the saline-filled ME: in contact with the TM; in the round window niche; or in the facial recess. As in Fig. 6 above, the location of the implant has no effect at low frequencies but a location-specific effect at 0.6 kHz and above: when in contact with the TM, the implant produces an increase in $|V_U|$ at nearly all frequencies above 0.6 kHz; when near the TM in contact with the round window, the implant increases $|V_U|$ up to 3 kHz; and when distant from the TM in the facial recess, the implant produces a resonant increase in $|V_U|$ at 0.8 kHz but no increase at higher frequencies (in fact, a slight reduction in $|V_U|$ in narrow frequency bands, e.g., 1–3 kHz; see discussion of Fig. 6 in Sec. 3.2). In general, the closer the implant is to the TM, the higher the frequency range over which it increases $|V_U|$.

Similar results were seen in all four ears, and statistics at audiometric frequencies are tabulated in Table 1. Inserting an implant into a saline-filled ME produced a significant increase in $|V_U|$ at 500 Hz and below, regardless of location. (As discussed later, the magnitude of these low-frequency improvements was often limited by the presence of residual air in our temporal bone preparation). At 1 kHz and above, an implant in contact with the TM produced a highly significant increase in $|V_U|$, while an implant not in contact with the TM produced a small change that was not statistically significant.

3.5. Effect of multiple implants

3.5.1. On TM—Given the similarity in improvements in V_U produced by air bubbles or implants (Fig. 6), we expected that increasing the number of implants in the ME should have the same effect as introducing a larger air bubble (Figs. 1C and 4). Again, for simplicity, we start in Fig. 9A with the effect of one or more implants on the TM in ear 32R. With no implants in the saline-filled ME, V_U is about -25 dB across frequency. At nearly all frequencies, $|V_U|$ increases when an implant is inserted into the ME, and $|V_U|$ increases approximately monotonically as the number of implants increases. This figure shows clearly that additional implants on the TM provide an additional increase in umbo velocity and presumably an additional benefit to hearing at all frequencies.

3.5.2. Not on TM—Fig. 9B shows the effect of one or more implants in the same ear but not in contact with the TM. As in Fig. 9A, $|V_U|$ increases monotonically at low frequencies as the number of implants increases. The frequency of the resonant peak in $|V_U|$ decreases as the number of implants increases, though the frequency of the antiresonance notch (see Sec. 3.2) remains constant. Consistent with Fig. 4A and in contrast with Fig. 9A, additional implants not on the TM do not increase high-frequency $|V_U|$.

3.5.3. On TM with additional implants not on TM—Once implants are in contact with the TM, additional implants elsewhere in the ME have positive effects. Fig. 9C shows $|V_U|$ in the saline-filled ME of ear 32R (black curve), with zero or two implants on the TM (solid lines), and with an additional 1, 2, or 3 implants in the facial recess (dot-dashed and dotted lines). Consistent with the results in Figs. 9A and 9B, additional implants not in contact with the TM have little effect at high frequencies but provide a substantial improvement in $|V_U|$ at low frequencies.

Similar results were seen in the other ears, and results in all ears are shown at representative low and high frequencies in Figure 10. Figs. 10A and 10B show the cumulative increase in $|V_U|$ at 250 Hz and 2 kHz, respectively, as additional implants were inserted into the ME: in contact with the TM (open circles), not in contact with the TM (filled triangles), or not on the TM with implants on the TM already (open squares). The lines linking the symbols indicate series in which implants were added to or removed from the ME one by one. Data from each ear are plotted with a unique line type (see figure caption for line code.) The features described in ear 32R in Fig. 9 were also seen in the other ears: (1) $|V_U|$ increased at low frequencies as the number of implants anywhere in the ME increased; (2) $|V_U|$ increased at high frequencies only when implants were in contact with the TM; and (3) once one or more implants were in contact with the TM, additional implants not in contact with the TM continued to increase $|V_U|$ at low frequencies but had no additional effect at high frequencies.

These results are summarized in Fig. 10C and 10D, which shows the mean $\pm$ s.d. of the $|V_U|$ increase for a given number of implants situated as described above (in contact with the TM, not in contact, or not on the TM with implants on the TM already) at 250 Hz and 2 kHz, respectively. The statistics of the effects of additional implants once an implant is in contact with the TM are listed at audiometric frequencies in Table 2. At 500 Hz and below (Fig.

10C), additional implants produce an increase in $|\mathbf{V}_U|$ that is generally statistically significant (Table 2), regardless of the implant location of the additional implant(s) (though the $|\mathbf{V}_U|$ increase with 1 or 2 additional implants in contact with the TM is statistically significant only at 125 Hz). At 2 kHz and above (Fig. 10D), the increase in $|\mathbf{V}_U|$ is not significant with additional implant(s) on the TM but is generally significant with additional implants elsewhere (not on the TM).

4. Discussion

4.1. Validity and limitations of test technique

4.1.1. Reduction in umbo velocity as an indicator of hearing loss—Umbo velocity is a useful and reliable indicator of sound conduction through the normal middle ear in human subjects and temporal bones (e.g., Goode et al., 1993; Huber et al., 2001; Chien et al., 2006, 2009; Rosowski et al., 2007). For changes in $\mathbf{V}_U$ by ME fluid, bubbles, or implants to be considered reliable indicators of changes in ME sound conduction or hearing, it must be shown that sound transmission between the umbo and the inner ear is not affected by ME fluid. Our earlier study (Ravicz et al., 2004) showed a good correlation between $|\mathbf{V}_U|$ reductions and hearing loss in a clinical population (taking into account possible low-frequency $|\mathbf{V}_U|$ reductions due to static ME pressure) but did not directly answer the question of whether ME fluid has similar effects on $\mathbf{V}_U$ and stapes velocity.

Other subsequently-published studies in which fluid was introduced into an otherwise healthy ME generally support the idea that the effect of ME fluid on ossicular transmission (stapes motion relative to umbo motion) is small, though results vary among studies. In human temporal bones, ME fluid produced a small decrease in ossicular transmission below 1 kHz and a small increase at higher frequencies in MEs in which the cochlea was drained (Gan et al., 2006)⁴, though another study (Dai et al., 2008) showed that umbo velocity reductions due to a combination of ME fluid and static pressure underestimated hearing loss in a clinical population in which most patients had a retracted TM. In animal studies, ME saline produced (a) roughly similar reductions in guinea pig umbo velocity and compound action potential between 1 and 15 kHz (Turcanu et al., 2009), (b) an increase in guinea-pig ossicular transmission below 3 kHz and above 20 kHz and no consistent change at intermediate frequencies (Guan and Gan, 2011)⁵, or (c) increases in chinchilla conductive hearing loss that were generally matched by reductions in umbo velocity across frequency (250–8000 Hz), though conductive hearing losses of greater than 10 dB were associated with umbo velocity reductions 6–7 dB smaller (Thornton et al., 2013)⁶.

In contrast, other animal studies in which otitis media was induced by inoculation with pathogens can provide more direct assessments of the effects on ME transmission, but results have been more variable, perhaps because due to other ME pathology produced by the infection. In guinea pigs, otitis media produced (a) small changes in ossicular transmission 3 and 7 days post-inoculation but a significant decrease between 1 and 12 kHz

⁴In Gan et al. (2006) this appears as a low-frequency *increase* and high-frequency *decrease* in the ratio of umbo displacement to stapes displacement.

⁵In Guan and Gan (2011) this appears as a low-frequency *decrease* in the ratio of umbo displacement to stapes displacement.

⁶Conductive hearing loss was evaluated by elevation of cochlear microphonic thresholds.

at 14 days post-inoculation (Dai and Gan, 2008) or (b) a reduction in ossicular transmission of up to 16 dB at 400 Hz and 10 dB at 11 kHz 3 days post-inoculation and an insignificant reduction between 200 and 600 Hz and up to a 13-dB reduction at 14 kHz (Dai and Gan, 2010)⁷. Once the ME static pressure was released and ME fluid was drained, (c) umbo displacements in guinea pig and chinchilla were 5–8 dB lower below 1 kHz than in control ears (Guan and Gan, 2013; Guan et al., 2014), but (d) residual reductions of umbo and incus displacements were similar (Guan and Gan, 2013). These differing results suggest that, in experiments involving ME infection, residual ME pathology complicates the determination of the effect of ME fluid on ME transmission.

Though there is a fair amount of variability among studies, the overall trend, especially in studies similar to this one, supports the idea that ME fluid has little effect on ME sound transmission. To within a few dB, changes in V_U by ME fluid, bubbles, or the implants described here are representative of changes in stapes velocity and hearing.

4.1.2. Temporal bone preparation as a model for a fluid-filled ME—In clinical cases of OME, the ME can become completely filled with fluid as metabolic processes remove oxygen from the ME (Sadé and Ar, 1997; Doyle, 2000). As discussed in Ravicz et al. (2004) and in Sec. 2.4 above, it was very difficult to remove all of the air from the ME in our temporal bone preparation. This residual air facilitated umbo velocity in the otherwise saline-filled ME. In two ears, by drilling out as many mastoid air cells as possible and/or exposing the specimen to vacuum, we were able to produce a 25–30 dB reduction in $|V_U|$ at all measured frequencies by filling the dry ME with saline (Fig. 3C). Such a reduction is substantial but less than the 40 dB hearing loss that can be seen clinically in OME (e.g., Merchant and Rosowski, 2003) and indicates that there was still a small amount of air trapped somewhere in the ME (Ravicz et al., 2004). In other ears, at frequencies below 1 kHz, $|V_U|$ reductions of only 20 dB or less could be achieved. This residual air increased the variability in the fluid-filled baseline V_U among ears, especially at frequencies below 1 kHz, which made the *increase* in $|V_U|$ produced by bubbles or implants in the saline-filled ME hard to quantify. In Sec. 4.4 below, we compare V_U to the typical hearing loss with otitis media to arrive at an estimate of the improvement provided by implants on umbo velocity and hearing.

In our preparation, the facial recess was drilled out to provide access to the ME, and 1–3 implants could be placed in the facial recess under the acrylic window that sealed the opening. In clinical practice, the facial recess is intact, leaving little space for implants between the TM and the bony wall around the facial nerve. Nevertheless, our preparation is useful for showing the effect of the location of an implant and highlights the importance of contact between an implant and the TM.

⁷Ossicular transmission was evaluated by the ratio of umbo displacement to round window displacement (Dai and Gan, 2008) or by the ratio of basilar membrane displacement at the cochlear apex or basal turn, respectively, to umbo displacement (Dai and Gan, 2010).

4.2. Comparison with previous results and models in fluid-filled middle ears

4.2.1. At low frequencies: Effect of air volume—Our results are quite similar to those from the 2004 paper. The air bubbles used in this study fill in the low- to moderate- V_{MEC} side of the graph shown in Fig. 11(a) of that paper (Fig. 1A here). The modifications to our technique, informed by our pre-2004 experiences, allowed us to achieve $|V_U|$ reductions by ME saline of 20–30 dB in three additional ears. This in turn enabled us to demonstrate the effect of a small bubble or single implant on V_U .

In addition, we modified the model presented in the 2004 paper to account for a residual compliance of 13 μ l equivalent volume in the “best” fluid-filled ears. The modified model sets a more representative lower bound to our low-frequency V_U data with bubbles (Fig. 5A) and better predicts the upper bound to the observed increase in $|V_U|$ at 250 Hz, as is seen in the comparison of the increased umbo velocity we observed at low frequencies with additional implants to the prediction of the 2004 model (Fig. 10A).

4.2.2. At high frequencies: Effect of air in contact with TM—In our previous investigation of the effects of ME fluid on ME input (Ravicz et al., 2004), we observed a roughly monotonic decrease in high-frequency $|V_U|$ as the portion of the TM covered with fluid increased (see Fig. 1B). In that investigation, fluid in contact with ~50% of the TM caused on average an 8-dB reduction in $|V_U|$ from the ME dry case, fluid in contact with 100% of the TM caused a 26-dB reduction, and only two intermediate points between 50% and 100% TM were measured in one ear. Our results with smaller air bubbles contacting the TM fill this intermediate range.

In this section we compare high-frequency $|V_U|$ in this study measured after the introduction of small bubbles and V_U data from the 2004 study with the percentage of the TM area contacted by *air* (as opposed to Fig. 1B, which plots %TM contacted by *fluid*). In this discussion, for V_U with bubbles, we define % TM_{air} as the percentage of the TM *area* contacted by air. As it was not possible to measure % TM_{air} directly, we computed % TM_{air} from the bubble volume using the assumptions that the bubble is spherical, the area of the bubble in contact with the TM is approximately equal to the bubble’s cross-section area, and the TM area is about 60 mm² (Wever and Lawrence, 1954).

Figure 11 is a linear plot of $|V_U|$ (as a ratio, not in dB) at 2 kHz with the ME filled with saline with bubbles from this study and with the ME completely or partly filled with fluid from the 2004 study, against % TM_{air} . A simple proportionality between % TM_{air} and $|V_U|$ is shown by the dashed line with slope = +1. This linear relationship explains 90% of the variance in the 2004 data (filled triangles), including $|V_U|$ at 100% TM_{air} , and 89% of the variance in the bubble data (open circles), which suggests that $|V_U|$ is approximately directly proportional to % TM_{air} . A straight-line fit to the 2004 data has a slope of +0.99 (correlation coefficient $R = 0.95$), and a straight-line fit to the bubble data has a slope of +0.93 ($R = 0.95$). In both studies, the ear was generally oriented as it would be in a seated subject; but in the 2004 study, the fluid was introduced through the Eustachian tube into the protympanum and contacted the posterior-inferior portion of the TM first, then the umbo, so any remaining air contacted the superior portion of the TM until the TM was completely

covered. In contrast, in the experiments described here, when an air bubble was introduced into the ME and contacted the TM, it was usually trapped inferior to the umbo (see Sec. 2.3.3). In summary, Fig. 11 shows that the residual high-frequency $|\mathbf{V}_U|$ in a ME with fluid is directly related to the amount of the TM contacted by air, regardless of whether the air is superior or inferior to the umbo.

In the 2004 paper, $|\mathbf{V}_U|$ was also measured in one ear (25A) with the ear oriented so the TM was inferior to the ME and the ear canal was pointing down. In this case, as fluid was instilled into the ME, it contacted the TM periphery first, then the central TM at the umbo; so the thickness (and therefore mass) of fluid on the TM when the TM was completely covered was less than when the ear was in its normal orientation. $|\mathbf{V}_U|$ in this case (open triangles) is substantially higher than that predicted by the linear relationship: the $|\mathbf{V}_U|$ for 0% TM_{air} (0.36; asterisk for 100% TM in Fig. 1B here and Fig. 11(d) of Ravicz et al., 2004) is much higher than $|\mathbf{V}_U|$ with the ear oriented normally (<0.1). This $|\mathbf{V}_U|$ of 0.36 corresponds to about 35% TM_{air} in the bubble data set, which suggests that the thin layer of fluid on the central TM at the umbo in this case had less effect than the thicker layer that covered the TM when the ear was in its normal orientation. Similarly, $|\mathbf{V}_U|$ was higher when air contacted 50% of the TM around the umbo (>0.8) than in this and all other ears in normal orientation (0.3–0.6) when fluid contacted the umbo.

The close fit of $|\mathbf{V}_U|$ and % TM_{air} in Fig. 11 to a simple proportionality suggests that the reduction in $|\mathbf{V}_U|$ is governed by a simple mechanism. Further study could define the governing mechanisms.

4.3. Effectiveness of implant in the presence of ME static pressure

Otitis media with effusion (acute or chronic) is often accompanied by a change in ME static pressure. The exudation of purulent fluid in acute OME causes an overpressure (positive pressure), while serous effusion is thought to be caused by ME underpressure (negative pressure; e.g., Sadé and Ar, 1997; Doyle, 2000; Bluestone and Klein, 2007). Previous studies in dry MEs have shown that ME over- or under-pressure reduces umbo velocity by 10–18 dB below 1–2 kHz but has little effect at higher frequencies (Murakami et al., 1997; Homma et al., 2010). A valid clinical question is whether the degree of restoration of $\mathbf{V}_U$ by the implant in the saline-filled but unpressurized ME will be maintained in the presence of ME underpressure.

Recent studies in animals of the effect of otitis media on umbo motion over the time course of a few days do not answer this question definitively. In an experiment in chinchillas (Guan et al., 2014) in which otitis media with effusion was induced and both ME fluid and alterations in ME static pressure developed, different results were obtained at different stages of the condition. After 4 days, the fluid filled approximately half of the ME cavity volume, and umbo motion increased substantially below 2 kHz after the ME was briefly vented to the atmosphere (thereby releasing any static ME pressure), which implies that ME static pressure contributed substantially to the overall reduction in umbo motion at low frequencies when the ear was partially filled with effusion. (Similar results were obtained in longer- and shorter-term studies in guinea pigs; Dai and Gan, 2008; Guan and Gan, 2013.) In contrast, after 8 days, when the ear appeared “nearly filled” with effusion, umbo motion

in chinchillas changed very little when the ME was vented but increased across frequency when the fluid was removed from the ME. The lack of effect of venting the ME suggests that, when effusion nearly or completely fills the ME, restoring ME air volume may be the most important treatment.

Studies of ME static pressure and ME fluid together in human temporal bones are also not definitive: recent studies (Gan et al., 2006; Dai et al., 2008) had the seemingly contradictory result that the effect of ME static pressure and fluid together on umbo motion was (i) smaller than ME static pressure alone at low frequencies (below 1 kHz) and (ii) smaller than fluid alone at higher frequencies. If true, this result suggests that ME static pressure will not adversely affect the functioning of the implant in a fluid-filled ME. Tests in patients with clinical OME will be necessary to confirm that the implant facilitates umbo velocity in the presence of ME static pressure.

4.4. Estimate of the effectiveness of the middle-ear implant in restoring hearing

As mentioned in Sec. 4.1 above, a limitation of our preparation was that we were unable to achieve a reduction in umbo velocity comparable to the clinically-observed hearing loss with OME of about 40 dB (because we were unable to remove a residual air volume of $\sim 10 \mu\text{l}$ from the preparation). As a consequence, the effect of a single implant in increasing umbo velocity in a fluid-filled ME described in Fig. 10 is probably an underestimate of the improvement provided by an implant in an effusion-filled ear. In Figure 12 we estimate the improvement in hearing that could be provided by implants by comparing $|\mathbf{V}_U|$ with one or more implants to a typical 40-dB hearing loss seen clinically with OME or COM.

Figure 12, which is formatted as an audiogram, shows $|\mathbf{V}_U|$ with one or more implants in ear 32R (which had the greatest reduction in $|\mathbf{V}_U|$ by saline). The $|\mathbf{V}_U|$ of 17–26 dB observed at audiometric frequencies with one implant on the TM (filled circles) suggests that, in a patient with a completely effusion-filled ME that produced a 40-dB conductive hearing loss, inserting one implant in contact with the TM provides, a 14–23 dB improvement in hearing from the 40 dB level. Similarly, inserting a second implant in contact with the TM further improves the predicted hearing level by another 5 dB, resulting in a 12–21 dB hearing loss (open circles). Additional implants (whether in contact with the TM or not) are predicted to provide further smaller but still clinically important improvements at 500 Hz and below (other open symbols), potentially reducing the 40-dB hearing loss to only 12–20 dB. The low-frequency improvements are slightly larger but still consistent with the predictions of the simple model (Ravicz et al., 2004; Fig. 1C; crosses) with an increasing number of implants of mean equivalent acoustic volume of $13 \mu\text{l}$: improvements of 10, 16, 19, 21, and 23 dB, respectively, from the non-aerated state. As long as ossicular motion is not impaired by the implants themselves, as many implants as possible should be introduced into an effusion-filled ME to maximize the improvement in low-frequency hearing.

5. Summary and conclusions

1. Even small amounts of air in an otherwise saline-filled middle ear increase umbo velocity in certain frequency ranges substantially, to levels only 10–15 dB lower than that in the dry middle ear.
2. The location of the air in an otherwise saline-filled middle ear influences the frequency range of umbo velocity increase: air in contact with the tympanic membrane increases umbo velocity at all frequencies, while air not in contact with the tympanic membrane increases umbo velocity only below about 800 Hz.
3. A novel compliant air-filled middle-ear implant has the same effect on umbo velocity as an equivalent amount of air in an otherwise saline-filled middle ear.
4. Inserting additional implants into the middle ear had the same effect as increasing the size of the air bubble.
5. These middle-ear implants could restore substantial hearing ability in patients with effusion-filled middle ears. Our recommendation to maximize the restoration of hearing is to insert 1–2 implants into the mesotympanum in contact with the tympanic membrane and as many as possible into other parts of the middle ear without hindering motion of the ossicles.

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APPENDIX A: Determination of implant equivalent acoustical volume

A small volume of air facilitates umbo velocity in a fluid-filled middle ear at low frequencies by increasing the acoustic compliance of the fluid-filled ME. The acoustic compliance is a measure of the compressibility of the air space at acoustic frequencies (above 20 Hz); and the compressibility is a measure of the change in volume in response to a pressure stimulus. The greater the ME compliance, the higher the TM and ossicular motion produced by a low-frequency sound at a particular level (e.g., Ravicz et al., 1992; Rosowski, 1994; Peake and Rosowski, 1997; Ravicz and Rosowski, 1997; Huang et al., 2000).

The compliance C of a small quantity of air is directly related to its volume V by

$$C = V / (\rho_0 c^2), \quad (\text{A.1a})$$

where ρ_0 is the density of air and c is the speed of sound (e.g., Beranek, 1986, Eq. 5.38). In this way, an acoustic compliance can be expressed in terms of its equivalent volume by rearranging Eqn. A.1a:

$$V = C \rho_0 c^2. \quad (\text{A.1b})$$

We use Equation A.1b to describe the performance of the ME implant in terms of its equivalent acoustical volume EAV , the volume of air that has the same compliance as the implant. Because the implant walls are less compliant than air, the EAV is always less than the actual implant volume.

Determination of the EAV of an implant involves two types of measurements: the actual volume of the implant $V_{Implant}$ and the acoustic admittance of a small test vial (volume $\sim 100 \mu\text{l}$) with and without the implant present. The actual volume was measured by instilling water into the test vial with a microsyringe (Hamilton, Reno, NV) both with the implant in the vial and without. Repeated measurements established the precision of this technique at about 10% of the implant volume.

The acoustic admittance Y of the test vial was measured with a specially designed acoustic source (Rosowski et al., 2006) comprising a small earphone (Knowles ED-1913 hearing aid receiver; Elk Grove, IL), microphone (Knowles EK-3027), and probe tube. The acoustic source was calibrated by measuring its response to an acoustic stimulus when coupled to various reference cavities of known dimensions, using the technique of Lynch et al. (1994; Ravicz et al., 1992). The sound stimulus for these tests was a broadband acoustic chirp comprising 512–600 frequencies between 24 Hz and 12.5–15 kHz. The chirp was generated, the microphone response was measured, and computations were performed with the same software and hardware used for measurements as described in the Methods.

At low frequencies, the admittance of the vial is due primarily to the compliance of the air in the vial. The compliance C_{Vial} of the empty test vial was computed from its admittance $\mathbf{Y}_{Vial}$ over a 100-Hz range around 460 Hz (average over 413–512 Hz) by

$$C_{Vial} = \text{Im} \{ \mathbf{Y}_{Vial} \} / 2\pi f, \quad (\text{A.2})$$

where $\text{Im} \{ \mathbf{Y}_{Vial} \}$ is the imaginary (out-of-phase) part of the complex admittance $\mathbf{Y}_{Vial}$ and f is frequency. The acoustical volume of the empty vial V_{Vial}^A computed from C_{Vial} by Eqn. A.1b above was within a few percent of its actual volume measured with the microsyringe.

Similarly, the acoustical volume of the test vial with the implant present $V_{Vial+Implant}^A$ was computed from its admittance. Because $|\mathbf{Y}_{Vial}|$ was near the limits of the capabilities of the acoustic source and the acoustic source calibration varied slightly during a measurement session, each acoustic measurement with an implant in the vial was preceded and followed by a measurement with the cavity empty. Overall, variations in V_{Vial}^A during a measurement session were less than 1%.

The acoustical volume $V_{Vial+Implant}^A$ describes the remaining air volume within the test vial $(V_{Vial}^A - V_{Implant})$ plus the EAV of the implant, such that:

$$V_{Vial+Implant}^A = (V_{Vial}^A - V_{Implant}) + EAV. \quad (\text{A.3a})$$

Rearranging, the equivalent acoustical volume is

$$EAV = V_{Vial+Implant}^A - \left(V_{Vial}^A - V_{Implant} \right). \quad (A.3b)$$

An implant of actual volume 20 μl and EAV of 13 μl should have the same effect on umbo velocity in a fluid-filled ME as an air bubble of 13 μl . An implant EAV much lower than 50% of the actual volume would be of limited acoustical consequence or utility. Implant EAV s were found to be between 50 and 80 percent of their actual volume.

List of abbreviations

<i>C</i>	Compliance of a small quantity of air
<i>C_{Vial}</i>	Compliance of the air in the small measurement vial
<i>c</i>	Speed of sound
COM	Chronic Otitis Media
<i>EAV</i>	Equivalent Acoustic Volume of implant
<i>f</i>	Frequency
ME	Middle Ear
N	Number of trials
OME	Otitis Media with Effusion
<i>p</i>(0)	Probability that the null hypothesis is true
P_{EC}	Sound pressure in the ear canal
<i>R</i>	Correlation coefficient
ρ_0	Density of air
TM	Tympanic Membrane
%<i>TM_{air}</i>	Percentage of TM area contacted by air
<i>V</i>	Volume of a small quantity of air
<i>V_{Implant}</i>	Volume of an implant
<i>V_{Vial}</i>^A	Acoustic volume of the small measurement vial
<i>V_{Vial+Implant}</i>^A	Acoustic volume of the small measurement vial with an implant inside
<i>V_{MEC}</i>	Volume of middle-ear cavity
% <i>V_{MEC}</i>	Percentage of middle-ear cavity volume filled with air
<i>V_U</i>	Umbo velocity
ΔV_U	Change in <i>V_U</i> from the normal condition
<i>Y</i>	Acoustic admittance
<i>Y_{Vial}</i>	Acoustic admittance of the air in the small measurement vial

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Research highlights

- Saline-filled human cadaver middle ears modeled otitis media with effusion (OME).
- Air in a saline-filled cadaver middle ear increases umbo velocity substantially.
- A novel air-filled middle-ear implant acts as a comparable air bubble.
- Umbo velocity increases more above 1 kHz when the implant contacts the TM.
- These implants could improve hearing in patients with non-aerated middle ears.

Fig. 1.

(A) and (B) The reduction in sound-induced umbo velocity produced by infusing fluid into the middle ear of nine normal human temporal bones (adapted from Ravicz et al., 2004, Fig. 11(a), 11(d)). (A) At low frequencies (around 150 Hz), as a function of the residual middle-ear air volume % V_{MEC} . The standard deviation (s.d.) around the mean with the ME dry is shown by the open diamond and error bars. The solid line is the reduction predicted by the ME model in Ravicz et al. (2004, Fig. 15). (B) At high frequencies (around 2 kHz), as a function of the percent of the tympanic membrane contacted by saline % TM . Umbo velocity

reduction when the ME was filled with additional saline after 100% of the TM was covered is plotted at the right for comparison. Symbols as in Panel A; means of 0% *TM*, 50% *TM*, 100% *TM*, and 100% *TM* with increasing amounts of saline elsewhere in the ME are shown as open squares. (C) Prediction of the Ravicz et al. (2004) model of the low-frequency umbo velocity reduction with air bubbles of various volume in the saline-filled ME (circles).

Fig. 2.

(Color online) (A) Schematic of a horizontal section of a typical temporal bone, showing preparation and setup. A sound-pressure source was coupled to the sealing ring to generate sound pressure in the ear canal. A metal sleeve was installed in the bony Eustachian tube; in ear 28B, a second sleeve was installed in the ear-canal wall to aid in placing a microphone probe tube near the umbo. Sound pressure P_{EC} was measured in the ear canal near the umbo. Umbo velocity V_U was measured with a laser-Doppler vibrometer whose laser beam was focused through a window in the ear canal onto a target on the umbo. The vibrometer

head was 15–25 cm from the target. Normal saline was introduced from the calibrated syringe into the middle ear through a fill tube attached to the Eustachian tube sleeve. The fluid level was monitored and air was allowed to escape through windows in the antrum (not shown) and facial recess. (B) Implants (yellow) were inserted into the ME through the windows. The schematic shows one implant placed on the surface of the inferior TM and a second placed in the RW niche. (C) Sketch of air-filled implant. Dimensions in mm.

Fig. 3.

(Color online) (A) Umbo velocity $\mathbf{V_U}$ (normalized by sound pressure near the TM $\mathbf{P_{EC}}$) measured in four ears with the middle ear dry and sealed (as in the normal ear). Each curve is the mean of 11 (28B) or 2–4 measurements (others). (B) The range of $\mathbf{V_U}$ in the four ears compared with the means from Ravicz et al. (2004, Fig. 9(a); solid line) and later studies: Nakajima et al. (2005; long-dash-dotted light line), Gan et al. (2006; dashed line), Dai et al. (2008; double-dot-dashed line), Homma et al. (2010; dashed line), and Zhang et al. (2014; dotted line) in temporal bones, and Rosowski et al. (2012; dot-dashed line) in human

subjects. Note that the Gan et al., Dai et al., and Zhang et al. data were originally presented as peak-to-peak displacement for a given sound pressure in dB SPL and have been converted to $\mu\text{m}\cdot\text{s}^{-1}\cdot\text{Pa}^{-1}$ for comparisons. Top: magnitude; bottom: phase. (C) “Best” |

V_U (greatest change in umbo velocity magnitude) by ME saline in each of the four ears (see legend in panel A). The greatest low-frequency reduction in $|V_U|$ was seen in ears 28B and 32R: approximately -30 dB. In two other ears (31R, 33R), low-frequency $|V_U|$ was about -20 dB.

Fig. 4.

(Color online) Mean change in umbo velocity ΔV_U in ear 32R with the ME filled with saline (the mean $\pm$ 1 s.d. of 11 measurements with no bubbles, dark shading) and with small bubbles of various sizes and locations in the saline-filled ME: (A) with 10–30 μ l bubbles in the facial recess not in contact with the TM (thin lines); (B) with 10–25 μ l bubbles in contact with the TM (thin lines). ΔV_U with a 20- μ l bubble in the facial recess (from panel A) is shown for comparison (light dotted-long-dashed line). Top: magnitude; bottom: phase.

Fig. 5.

(Color online) Change in umbo velocity $|\Delta V_u|$ in three saline-filled middle ears (28B: circles; 32R: squares; 33R: diamonds) with bubbles of various sizes in contact with the TM (open symbols) or not (closed symbols). The triangles plotted on the left axis of both panels show the mean $|\Delta V_u|$ in the three ears with no bubbles. (A) At a low frequency (250 Hz). The solid line is the prediction of the simple ME fluid model from Ravicz et al. (2004, Fig. 11(a)); the dashed line includes the effect of a residual compliance with equivalent volume of 13 μl described in that study (Fig. 15). (B) At a high frequency (2 kHz).

Fig. 6.

(Color online) Equivalence of the effect of a 20- μ l air bubble and two implants (equivalent air volume of 25 μ l) on ΔV_U in the saline-filled middle ear of ear 32R. (A) Located in contact with the TM. The magnitude and frequency dependence of ΔV_U with two implants contacting the TM (dot-dashed line) are similar to ΔV_U with a 20- μ l air bubble contacting the TM (dashed line). (B) Located in the facial recess far from the TM. ΔV_U with two implants not in contact with the TM (double-dot-dashed line) is similar to ΔV_U with a 20- μ l air bubble not in contact with the TM (dot-long-dashed line). ΔV_U with implants or air was higher at low frequencies than ΔV_U with neither implants nor air (solid line).

Fig. 7.

(Color online) Consistency of the effect on $|V_U|$ of six different implants placed individually into the saline-filled ME of ear 32R. The variation among implants (individuals: thin lines; mean $\pm$ s.d.: thick line and shading) is less than the increase in $|V_U|$ produced by any one implant (7–15 dB). The $|V_U|$ with no implants (ME filled with saline) is shown by the lower solid line.

Fig. 8. (Color online) Effect of the location of one implant on $|\mathbf{V}_U|$ in the saline-filled ME of ear 32R: $|\mathbf{V}_U|$ with the same implant in contact with the TM (dashed curve), in the RW niche (no TM contact; dotted curve), or in the facial recess (no TM contact; long-dash-dotted curve). $|\mathbf{V}_U|$ with no implant: solid line.

Fig. 9.

(Color online) Cumulative effect of additional implants in the saline-filled ME of ear 32R: (A) $|\Delta V_U|$ with 1 (light solid line), 2 (dot-long-dashed line), or 3 implants (dot-dashed line) in contact with the TM vs. 0 implants (solid black line). (B) $|\Delta V_U|$ with 1 (light solid line), 2 (dashed line), or 3 implants (dot-dashed line) not in contact with the TM (in facial recess). (C) $|\Delta V_U|$ with one (“2 TM + 1”; long-dash-dotted line), two (“+ 2”; double-dot-dashed line), or three implants (“+ 3”; dotted line) added in the facial recess with 2 implants already contacting the TM (light solid line).

Fig. 10.

(Color online) Cumulative effect of additional implants in saline-filled middle ears. (A) and (B) Cumulative increase in $|V_U|$ relative to the saline-filled ME as additional implants were added, as a function of the number and location of implants, at low (250 Hz) and high frequencies (2 kHz), respectively: All implants in contact with the TM (open circles); all not in contact with the TM (filled triangles); at least 1 implant in contact with the TM + more elsewhere in the ME (open squares). Some data are offset for clarity. Data from Ear 28B: dot-dashed lines; 31R: dashed lines; 32R: solid lines; 33R: long-dash-dotted lines. (C) and (D) Means and s.d.s of the increases in $|V_U|$ for all measurements in all four ears as a

function of the number and location of implants in the saline-filled ME, at 250 Hz and 2 kHz, respectively.

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Fig. 11.

(Color online) Relationship between $|\Delta V_U|$ at 2 kHz and the amount of air contacting the TM in the otherwise saline-filled ME in this study and a previous study (Ravicz et al., 2004). The horizontal axis $\%TM_{air}$ is the percentage of the TM area contacted by *air* (in contrast with Fig. 1B which shows the $\%TM$ contacted by *saline*); the left-hand axis is $|\Delta V_U|$ expressed as a ratio. In the 2004 study, air contacted the TM superior to the umbo (filled triangles) or, in one bone, a region around the umbo (open triangles). In this study, air bubbles in contact with the TM generally contacted the portion inferior to the umbo (open circles). For simplicity, the effective contact area between the bubble and the TM is assumed equal to the bubble cross-section area. The dashed line denotes a simple proportionality between $|\Delta V_U|$ and $\%TM_{air}$ (slope = +1).

Fig. 12.

(Color online) Estimated hearing levels with increasing numbers of implants in the non-aerated middle ear, plotted as an audiogram. The black dot-dashed line shows the typical 40-dB conductive hearing loss in non-aerated ears. Curves and symbols show estimated hearing loss with implants in the non-aerated ME: 1 implant in contact with the TM (solid line and closed circles), 2 implants in contact with the TM (dotted line and open circles), and 2 implants in contact with the TM with an additional 1, 2, or 3 implants not in contact with the TM (squares, triangles, and diamonds, respectively). Low-frequency hearing levels predicted by the model of Ravicz et al. (2004; see Fig. 1C), using an implant equivalent volume of 13 μl , are shown by black crosses at left, labeled with the total number of implants.

Increase in umbo velocity at audiometric frequencies produced by inserting a single implant into a saline-filled middle ear. $p(0)$ = probability that the implant and no-implant samples come from the same population, evaluated by Student's t -test. Statistical significance is $p(0) < 0.05$. The number of trials N encompasses measurements in all four ears. In each case, removing the implant returned the umbo velocity to within 1 dB of its initial value.

Table 1

Implant location	Freq. (Hz)	125	250	500	1000	2000	3000	4000
All (N=49)	Mean (dB)	1.3	3.4	4.7	4.1	7.3	8.4	11.0
	s.d. (dB)	2.7	3.9	4.4	4.4	7.8	7.4	9.2
	$p(0)$	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
On TM (N=37)	Mean (dB)	1.0	3.4	4.5	5.4	9.9	11.0	14.4
	s.d. (dB)	2.9	4.1	4.9	3.8	6.9	6.4	7.8
	$p(0)$	0.043	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Not on TM (N=12)	Mean (dB)	2.0	3.7	5.4	0.1	-0.7	0.1	0.4
	s.d. (dB)	1.5	3.7	2.6	4.0	4.0	2.7	3.0
	$p(0)$	<0.001	0.005	<0.001	0.92	0.56	0.89	0.68

Increase in umbo velocity at audiometric frequencies produced by introducing one or more additional implants into a saline-filled middle ear with one implant already in contact with the TM (includes data plotted in Fig. 10C and 10D). Statistical significance $p(0)$ and number of trials N as defined for Table 1. In each case, removing the implant(s) returned the umbo velocity in the saline-filled ME to within 1 dB of its initial value.

Table 2

Location of additional implant	Freq. (Hz)	125	250	500	1000	2000	3000	4000
On TM:								
1 additional (2 total; N=14)	Mean (dB)	2.9	1.0	0.06	2.5	2.0	1.8	2.5
	s.d. (dB)	3.4	2.3	4.8	3.3	4.7	5.9	6.5
	$p(0)$	0.008	0.13	0.96	0.012	0.13	0.27	0.18
2 (N=5)	Mean (dB)	3.8	2.1	-0.9	2.7	1.3	0	0.6
	s.d. (dB)	1.3	2.2	4.9	2.3	1.9	3.2	5.0
	$p(0)$	0.003	0.1	0.7	0.06	0.19	0.97	0.8
Elsewhere in ME:								
1 additional (N=11)	Mean (dB)	4.6	6.0	3.5	2.8	3.7	3.7	6.7
	s.d. (dB)	3.0	4.4	4.2	3.1	4.6	6.1	5.7
	$p(0)$	<0.001	0.001	0.02	0.013	0.025	0.072	0.003
2 (N=6)	Mean (dB)	3.6	2.5	3.1	1.7	0.1	4.3	5.0
	s.d. (dB)	1.4	1.9	1.2	1.3	3.6	1.5	4.0
	$p(0)$	0.0015	0.024	<0.0015	0.025	0.93	<0.001	0.028
3 (N=5)	Mean (dB)	3.8	3.7	6.1	3.6	3.9	6.6	7.1
	s.d. (dB)	3.1	3.0	4.3	1.6	5.9	8.0	5.5
	$p(0)$	0.053	0.049	0.035	0.007	0.21	0.14	0.045
4 (N=7)	Mean (dB)	4.5	7.6	2.3	2.5	6.5	6.9	9.6
	s.d. (dB)	3.1	4.6	3.9	3.7	5.4	6.8	6.1
	$p(0)$	0.008	0.005	0.16	0.12	0.02	0.037	0.006