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Research paper

A novel perfusion-based method for cochlear implant electrode insertion

Sushrut Kale [a, *], Vanessa M. Cervantes [a], Mailing R. Wu [a, b], Dominic V. Pisano [a], Nakul Sheth [a], Elizabeth S. Olson [a, b]

[a] Department of Otolaryngology-Head & Neck Surgery, Columbia University, New York, NY 10032, USA
[b] Department of Biomedical Engineering, Columbia University, New York, NY 10025, USA

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ABSTRACT

A cochlear implant (CI) restores partial hearing to profoundly deaf individuals. CI electrodes are inserted manually in the cochlea and surgeons rely on tactile feedback from the implant to determine when to stop the insertion. This manual insertion method results in a large degree of variability in surgical outcomes and intra-cochlear trauma. Additionally, implants often span only the basal turn. In the present study we report on the development of a new method to assist CI electrode insertion. The design objectives are (1) an automated and standardized insertion technique across patients with (2) more apical insertion than is possible by the contemporary methods, while (3) minimizing insertion trauma. The method relies on a viscous fluid flow through the cochlea to carry the electrode array with it. A small cochleostomy (~100–150 um in diameter) is made in scala vestibuli (SV) and the round window (RW) membrane is opened. A flow of diluted Sodium Hyaluronate (also known as Hyaluronic Acid, (HA)) is set up from the RW to the SV opening using a perfusion pump that sets up a unidirectional flow. Once the flow is established an implant is dropped into the ongoing flow. Here we present a proof-of-concept study where we used this technique to insert silicone implants all the way to the cochlear apex in rats and gerbils. In light-microscopic histology, the implantation occurred without cochlear trauma. To further assess the ototoxicity of the HA perfusion, we measured compound action potential (CAP) thresholds following the perfusion of HA, and found that the CAP thresholds were substantially elevated. Thus, at this point the method is promising, and requires further development to become clinically viable.

1. Introduction

A cochlear implant (CI) restores partial hearing to profoundly deaf people who do not benefit from conventional hearing aids. A CI device consists of an implantable receiver-stimulator circuit that is implanted in the human temporal bone and 22–24 electrodes that are implanted into the cochlea (inner ear) (Wilson and Dorman, 2008). CI electrodes are manually inserted into the cochlea. Anatomical constraints of the human temporal bone and the facial recess approach used for CI surgeries (e.g., Su et al., 1982) and variability in electrode array designs (Rebscher et al., 2008) can make the manual electrode insertion challenging. During the manual insertion process, surgeons rely on tactile feedback from the electrode tip to decide when to stop the insertion. Such surgical practice leads to high variability in surgical outcomes across patients (Finley et al., 2008) and a high degree of surgical trauma (e.g., Adunka and Kiefer, 2006).

Despite the efforts put into development of soft-surgery techniques (e.g., Lehnhardt, 1993; Friedland and Runge-Samuelson, 2009), a high-incidence of intra-cochlear insertion trauma persists. Cochlear trauma can range from small displacements of basilar membrane to more severe trauma such as fracture of the osseous spiral lamina and invasion of scala vestibuli by the electrode array, irrespective of the electrode-array designs (e.g., Briggs et al., 2001; Eshraghi et al., 2003; Adunka and Kiefer, 2006; Roland and Wright, 2006; Rebscher et al., 2008). Such severe trauma to delicate cochlear structures can lead to a loss of surviving spiral ganglion cell (SGC) bodies (Leake et al., 1999) and can potentially

* Corresponding author. 630 W 168th Street, P&S 11-452, New York, NY 10032, USA. Tel.: +1 212 305 3993.
E-mail address: sk3646@cumc.columbia.edu (S. Kale).

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contribute to poor speech recognition (Finley et al., 2008). Although the properties of electrode arrays such as electrode stiffness, length and curvature play a role in causing intracochlear trauma, studies suggest that the insertion-related trauma results from the force exerted by the electrode array on intracochlear structures due to the manual nature of the insertion (Eshraghi et al., 2003; Wardrop et al., 2005a, 2005b; Zhang et al., 2006). It has been shown that the performance of an individual surgeon with one type of CI device is not predictive of his/her performance with another type of CI device (Rebscher et al., 2008), which can lead to variability in surgical outcomes across patients. Finley et al. (2008) reported a large variability in insertion depth and electrode array location (i.e., ST vs. SV) across 14 patients using the same device type, which was associated with variability in their speech recognition performance. Full insertions reported in the literature even in normal cases range from 350° to 800° (reviewed by Boyd, 2011). In addition to this high variability in surgical outcomes, there is a lack of consensus regarding the cochleostomy location for electrode array insertion (Adunka and Buchman, 2007) and there appears to be a growing interest in round-window based insertion to minimize the trauma (Adunka et al., 2006; Adunka, 2010; Souter et al., 2011). Overall these studies establish a clear need for a new technique for electrode array insertion that would minimize intracochlear trauma and would be standardized across patients to achieve uniform surgical outcomes. Indeed, relatively elaborately engineered methods for reducing cochlear trauma are under development, such as CIs that sense and respond to contact forces, and would be inserted robotically (Zhang et al., 2006).

In contemporary surgical technique, it is often difficult to achieve electrode insertion deeper than the first basal turn even if the cochlea is anatomically normal (Lee et al., 2011). Incomplete insertion may create a mismatch between cochlear place and frequency. Improving the cochlear place-frequency map matching improves speech recognition (e.g., Fu and Shannon, 1999; Baskent and Shannon, 2004) and deeper apical insertion has been shown to improve pitch perception (Deman et al., 2004). However, intracochlear trauma associated with deeper insertion often outweighs the benefits of deeper insertion (Adunka and Kiefer, 2006). Hence, plausibility and benefits of apical stimulation remain less understood due to lack of a technique that will result in both deep apical insertion and little or no trauma to cochlear structures.

An increasing number of patients with profound high-frequency hearing loss but some residual hearing at low frequencies are being fitted with CIs in conjunction with hearing aids. These patients receive electrical stimulation at high frequencies and acoustic stimulation at low frequencies via hearing aids (Gantz and Turner, 2003; von Ilberg et al., 2011). For combined electrical-acoustical stimulation to work, a necessary prerequisite is to be able to preserve residual low frequency hearing. Significant efforts have been directed at preserving residual hearing in these patients following cochlear implantation. However, complete and long-term preservation of residual hearing remains a challenge and appears to be dependent on the surgeon's experience with the soft surgery technique (Balkany et al., 2006; Adunka, 2010). There are several factors underlying the loss of residual hearing. Studies have shown that manual insertion results in direct tissue trauma both acutely as well as chronically, in that it can trigger molecular events for future cell deaths and loss of residual hearing (Eshraghi, 2006).

In the present study we have introduced a new method for CI electrode insertion. The objective of the new method is to minimize insertion related trauma, standardize surgical outcomes across patients and achieve more apical electrode insertion than possible by the contemporary techniques. The technique is still evolving, with the long-term goal of hearing preservation. The technique relies on perfusion of a viscous biocompatible fluid through the cochlea to perform electrode insertion. The technique is at the proof-of concept stage, demonstrated in-vivo in gerbils and post-mortem in rats, and requires further research and development to realize clinical viability.

2. Methods

2.1. General methods

In the present study we have proposed a novel CI electrode insertion method assisted by flow of a viscous fluid through the cochlea. The fundamental principle behind the insertion technique is to set-up a unidirectional fluid flow from the round window to a small opening made in scala vestibuli (SV). Once the fluid flow is set up, CI electrodes are introduced in the ongoing flow and are flowed into the cochlea. In this proof of concept study we used mock CI electrodes made of silicone rubber, custom made in the lab. At the onset of the project we experimented with several fluids such as glycerin, mineral oil, saline, artificial perilymph (AP) and hyaluronic acid (HA), commercially available as Healon, Abott Medical Optics, Santa Ana, CA). During the pilot experiments we observed that the mock electrodes did not move with AP or saline flow and a viscous fluid was necessary. HA was selected (Briggs et al., 2001), as it is FDA approved and is routinely used as a lubricant in CI electrode insertion surgeries and in joint and eye surgeries.

2.2. Making of mock electrodes and fluid carriers

Mock CI electrodes were made by injecting liquid silicone rubber (Plastil 71-40 RTV from Polytek, Easton, PA) into glass capillaries ~4 cm long. Silicone was then cured for ~24 h and glass capillaries were later broken to remove flexible, solid silicone cylinders that were then cut in 10 mm lengths to make mock CI electrodes. (More recently, the injection molding was done into rubber tubing rather than glass capillaries, which makes removal easier.) Mock CI electrodes had either 98 μm or 180 μm diameter and the silicone had been dyed to make the implants visible through de-calcified cochleae following the insertion. Commercially available Healon, with a composition of 1% HA was diluted 1:1 with AP prepared in the lab to make 0.5% HA solution. AP had the following composition: NaCl 125 mM, KCl 3 mM, $NaHCO_3$ 25 mM, $CaCl_2$ 1.3 mM, $MgCl_2$ 1.2 mM and NaH_2PO_4 0.75 mM; and had a pH of 7.4. 0.5% HA solution was used as a carrier for mock electrodes in all the experiments. A 0.5% HA solution has a viscosity of ~1 Pa-s at a shear rate of 10 s^{-1}, which was – the rate used here (Maleki et al., 2007). This is in contrast to the ~1 mPa-s viscosity of water (which, being a Newtonian fluid, has a viscosity that does not depend on shear rate).

2.3. Electrode insertion methods

Initially mock electrodes were injected into cochlea with the help of a syringe filled with the HA solution. The syringe tip holding the mock electrode was sealed to the round window (RW) using cyanoacrylate glue or dental cement and a small opening in SV adjacent to the stapes served as an outlet. The RW and the neighboring area were filled with the HA solution to prevent air bubbles from entering the cochlea. Although with this method we could insert the mock electrodes deeply into cochlea, the method was discarded, as the RW sealing step was difficult and traumatic to the cochlea in some cases. In the next stage of development we tried pulling the mock electrodes into the cochlea using a 'reverse perfusion' technique. In this method, the perilymph was removed from the cochlea via the SV hole using a perfusion pump while being continuously replaced with HA solution via the RW. Mock electrodes were introduced in the flow using a syringe after visually confirming the inflow of HA solution into the RW.

Fig. 1A shows a gerbil RW with the RW membrane opened and a small hole (~150 μm) made in SV. Fig. 1B shows a syringe filled with HA solution positioned over the RW. A small glass capillary was sealed within the SV hole using soft dental cement and was used for the removal of perilymph. Since the RW was open during the perfusion, there was no significant pressure buildup inside the cochlea. Although this insertion method could produce deep insertions through several turns, it was not reliable since the successful insertion depended critically on how the electrodes were introduced in the HA solution inflow. Introducing the mock electrodes with a large pool of HA solution in the RW resulted in mock electrodes making a loop in the RW. On the other hand, if the electrodes were introduced while the HA solution was draining from the RW, air bubbles could be introduced into the cochlea. Large flow rates (24–50 μL/min) were needed to pull the mock electrodes into the cochlea. Data from cochleae implanted post-mortem using this method is shown in the results section.

To overcome the difficulties faced with the methods described above, we combined the injection and reverse perfusion method. A schematic of the existing method is shown in Fig. 2. In this method we introduced the mock electrode in a tube labeled 'the implant feeding line' through a valve in the back of the tube, so there was a column of HA solution preceding and following the implant. The implant feeding line was sealed within the RW using either an inflatable catheter balloon or soft dental cement and another glass capillary was connected to the SV hole. Both the tubes were attached to the perfusion pump so that removal of the perilymph from SV was synchronized with the inflow of HA from the round window. This method set up a unidirectional flow from the RW to the SV hole and also did not require mock electrodes to be introduced in the flow manually. With the mock electrode in the flow prior to starting the inflow of HA and synchronized inflow and outflow it was easier to insert the mock electrode and the method was more reliable. However, still quite high flow rates (~24 μL/min) were used for insertion. This method was implemented in three gerbils within 24–48 h post-mortem.

2.4. Assessing the ototoxicity of HA

In three gerbils, mock electrodes were inserted in-vivo using the reverse perfusion technique discussed above. However, following the electrode insertions we observed extreme hearing loss. Hence, to dissociate the loss of hearing caused by the mock electrode itself from that caused by the use of HA, we conducted a separate set of experiments to assess HA ototoxicity. The effect of HA perfusion on the cochlea was assessed using measurements of compound action potential (CAP) thresholds and/or endocochlear potential in a separate set of in-vivo experiments. 0.5% HA was perfused through cochleae using the reverse perfusion technique. The HA flow-rate was ~24 μL/min for these experiments. The CAP thresholds were measured right after opening the bulla i.e., the baseline condition, after the cochleostomy and following the HA perfusion. The CAP

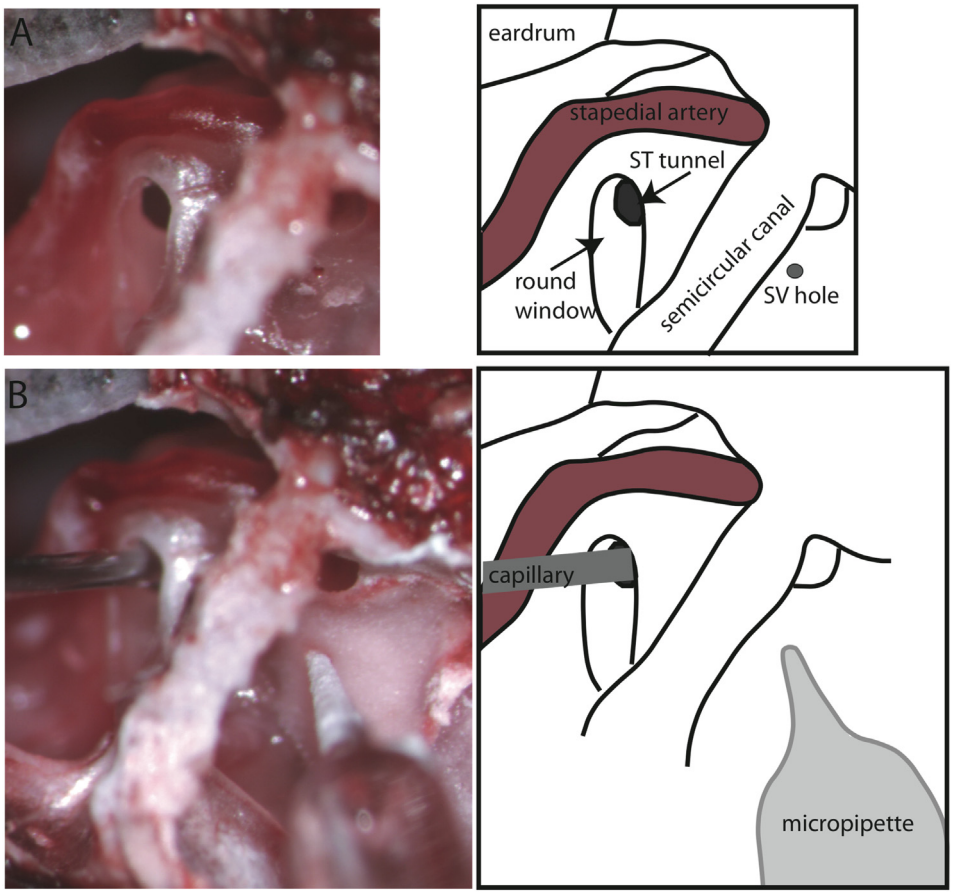

Fig. 1. A: View of the very basal cochlea. In the foreground is the lateral semicircular canal, and at the top of the panel the eardrum is visible. The gerbil has a prominent stapedial artery that lies above the round window opening. Cochleostomy (SV hole) and view of the Scala Tympani (ST) through opened round window membrane. B: Set-up for electrode insertion showing micropipette sealed to SV hole and capillary holding the mock implant in the RW above ST. The thumbnails to the right of the photographs clarify the description.

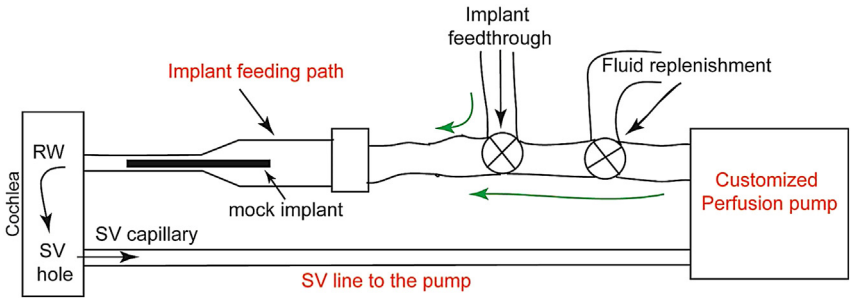

Fig. 2. Basic schematic of the tool used to implement perfusion based insertion.

stimulus was composed of 3 ms long tone pips presented every 12 ms, with alternating polarity to eliminate most of the cochlear microphonic from the averaged responses. CAP thresholds were collected for 16 frequencies ranging from 0.5 kHz to 40 kHz and compared across conditions.

2.5. Histological preparation and assessment

A subset of the implanted cochleae was examined histologically. After euthanasia, these cochleae were isolated and removed intact from the temporal bone. Fixative (2.5% glutaraldehyde, 1.5% formaldehyde in 0.065 M phosphate buffer) was gently perfused through the cochlea. The excised cochleae were then immersed in fixative for 24 h. The cochleae were decalcified in a 120 mM EDTA, pH7 solution over five days and washed in phosphate buffer. After decalcification the cochleae are quite transparent and for some the histological processing ended at this point. Others were further prepared for microscopic evaluation. These cochleae were then immersed in 0.1% Osmium Tetroxide for 30 min, and then washed with phosphate buffer. They were dehydrated with increasing concentrations of ethanol before being permeated with increasing concentrations of Epon 812 epoxy resin in propylene oxide. The specimens were embedded in fresh Epon resin, placed in a vacuum for 24 h and then a 60 °C oven for 24 h. 1.5 micrometer thick sections were mounted on glass slides, stained with Toludine blue and examined by light microscopy.

3. Results

3.1. Fluid assisted insertion resulted in very deep electrode insertion

Fig. 3 shows images of decalcified cochleae following implant insertion. These cochleae were implanted post-mortem with the mock electrodes using either the reverse perfusion method alone (Fig. 3A) or a combination of reverse perfusion and forward injection (Fig. 3B), using the tool described in the methods section. The dark band seen in both the panels is the silicone implant that was inserted all the way to the apex with both these methods. Fig. 4A–C (top row) shows histological images of gerbil (Fig. 4A) and rat cochleae (Fig. 4B and C) implanted with silicone implants of different diameters using the perfusion method. An implanted gerbil cochlea is shown in Fig. 4D after decalcification. It can be seen that the mock electrode has reached all the way to the apex. In the bottom row, sketches of the cochlear photos shown in the top and the middle row are shown for clarity. White circles in Fig 4 (top and middle row) are the cross-sections of the mock electrode. The inset in Fig. 4A shows a section of the BM and organ of Corti (OC) that is in the vicinity of the mock electrode. We did not see any overt damage to the basilar membrane and the organ of Corti following the insertion. We did not specifically evaluate the structural integrity of the hair cells. These results demonstrate the potential of the fluid-assisted insertion method to achieve deep and atraumatic insertions.

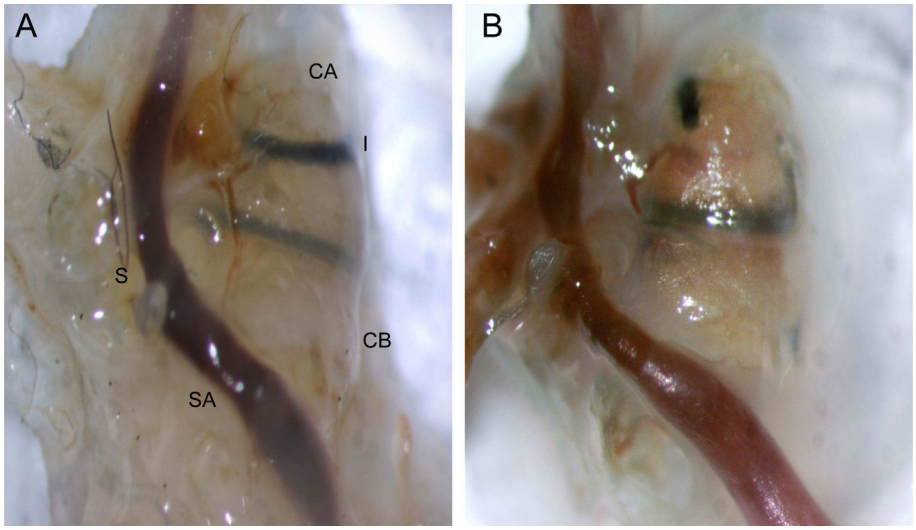

Fig. 3. Gerbil cochleae implanted with mock implants using the reverse perfusion method (A) and using the tool based on uni-directional flow (B). CA: cochlear apex, I: dark colored implant, CB: first basal turn, SA: stapedial artery and S: stapes neck.

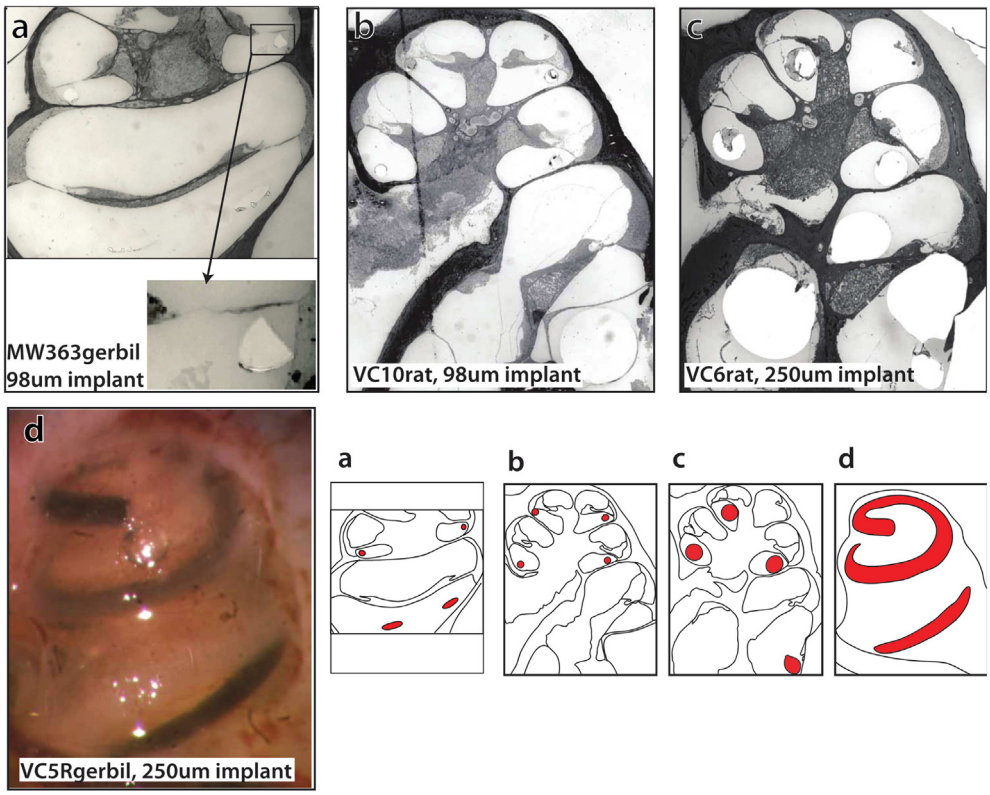

Fig. 4. Fresh post-mortem rat and gerbil cochleae stored in the refrigerator for one – several days were used to develop the perfusion-implantation technique. Implant diameters are indicated in the panel labels. The implant carrier was 0.5–1% hyaluronic acid. (a) Cochleae implanted with the reverse perfusion method (implant drawn into ST through the round window opening by the flow of HA as fluid was withdrawn from a cochleostomy near the stapes). The boxed region is expanded in the lower panel. (b–d) Earlier preparations, implanted via forward injection-perfusion through the round window opening. The placement of the implants is represented in red in the image thumbnails. Histological sections in (a–c) demonstrate that the integrity of the basilar membrane was preserved and the implant remained in ST. (The sectioning process removed the silicone implant from the embedded sections, and therefore only the implant shape remains. Air bubbles are evident in the base of panels b&c, and might have developed during implantation, or during embedding.) (d) Decalcified implanted gerbil cochlea. The implant is dyed black and can be seen coiling around the modiolus. The 250 um diameter implant of this experiment would almost fill ST of the gerbil (Plassmann et al., 1987) and thus this specimen might have sustained damage to the basilar membrane when the implant flowed all the way to the cochlear apex, but this specimen was not evaluated histologically.

3.2. CAP thresholds were elevated following sodium hyaluronate (HA) perfusion

Fig. 5 shows CAP thresholds measured in six gerbil ears before and after perfusion with HA. The perfusion method and perfusion parameters matched those used for the implant insertion, but no implant was inserted. Fig. 5A shows the CAP thresholds just after opening the bulla, our baseline (control) condition. Opening the round window membrane and making a small cochleostomy in SV did not increase CAP thresholds, indicating that the cochleostomy was not very traumatic. However, following HA perfusion, CAP thresholds were elevated (Fig. 5C). With the exception of one animal, the threshold elevation ranged from 45 to 90 dB relative to the post-cochleostomy thresholds (Fig. 5D). Salt et al. (2009) measured CAP thresholds following HA injections into the apex of the cochlea. They observed CAP threshold shifts of 40–80 dB following the injections, which was consistent with our observations. However, in those studies CAP thresholds returned to the baseline condition when the injected gel was removed. In contrast we did not observe any reversal in elevated CAP thresholds in the present study despite waiting for 1–2 h following the perfusion.

Fig. 6 shows CAP thresholds following the perfusion by AP using the same reverse perfusion technique and same flow parameters. Generally speaking thresholds were not much changed following AP perfusion. In one gerbil (indicated by red), post-cochleostomy thresholds (Fig. 6B) were elevated by 35–45 dB at high frequencies relative to the baseline condition (Fig. 6A). Baseline data for one gerbil (shown in blue, Fig. 6B) was not collected. However, post-cochleostomy thresholds in this animal were higher than those observed in the six animals previously shown (in Fig. 5B). Hence, it is likely that of the nine animals, two lost some hearing following the cochleostomy. CAP thresholds were mildly elevated relative to the baseline conditions in two of the three animals with one animal showing no negative effect of AP perfusion (Fig. 6C and D). For frequencies below 6 kHz, the threshold elevation following AP perfusion was very small compared to that following the HA perfusion (compare Figs. 5C and 6C).

For four of the six gerbils perfused with HA we waited for ~2 h and measured CAP thresholds ~2 h later. The rationale was that the cochlea would rid itself of HA replacing it with perilymph. Fig. 7 compares shifts in CAP thresholds measured immediately following HA perfusion (Fig. 7A) to those measured ~2 h later (Fig. 7B). Despite some qualitative evidence of HA replacement by perilymph (based on a rough measure of the viscosity of the fluid in the RW opening), CAP thresholds did not return to the baseline condition. In two of the four animals we re-perfused the cochleae with AP after waiting for two hours. The rationale was that the AP would clear the residual HA from the cochleae and might bring the CAP thresholds back to the baseline. However, CAP thresholds did not return to baseline. These results suggest that the perfusion with

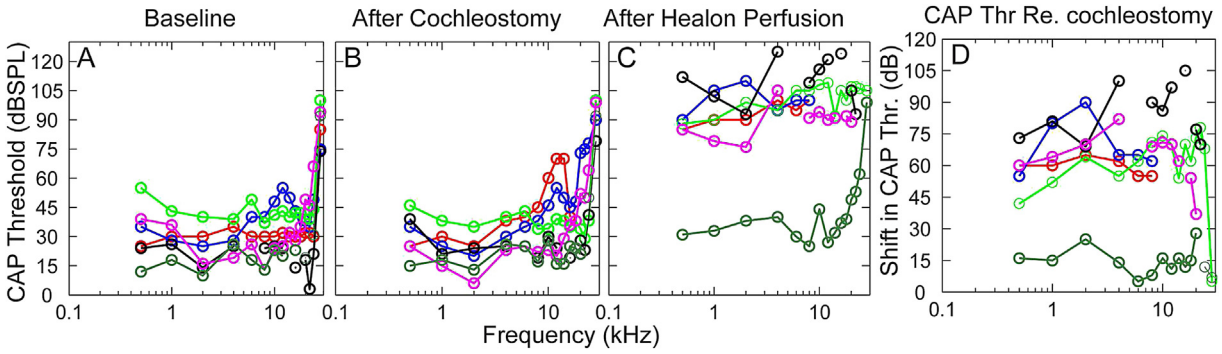

Fig. 5. Each color indicates the data obtained from one gerbil across four conditions. A: Baseline CAP thresholds from 6 normal cochleae. B: After opening the RW membrane and making SV hole. C: After reverse-perfusing 0.5% HA. D: CAP thresholds following the reverse-perfusion, relative to following the cochleostomy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

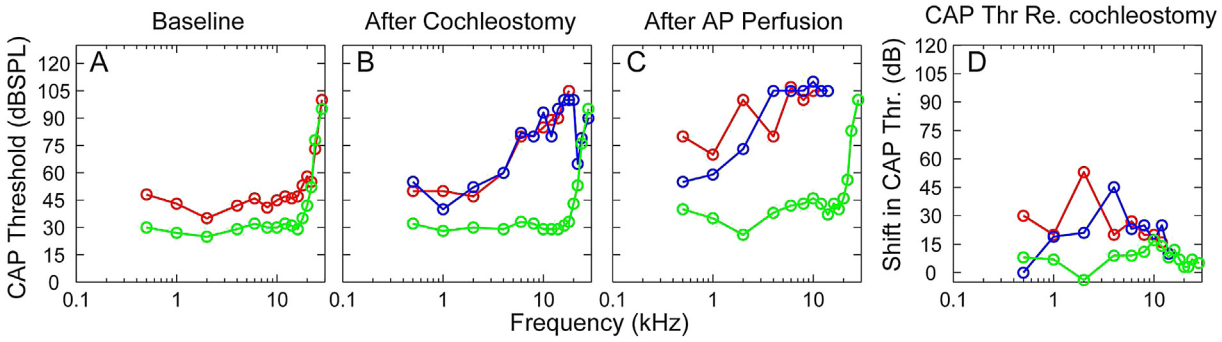

Fig. 6. Effect of AP perfusion using the implantation set up. The data shown is for three gerbils.

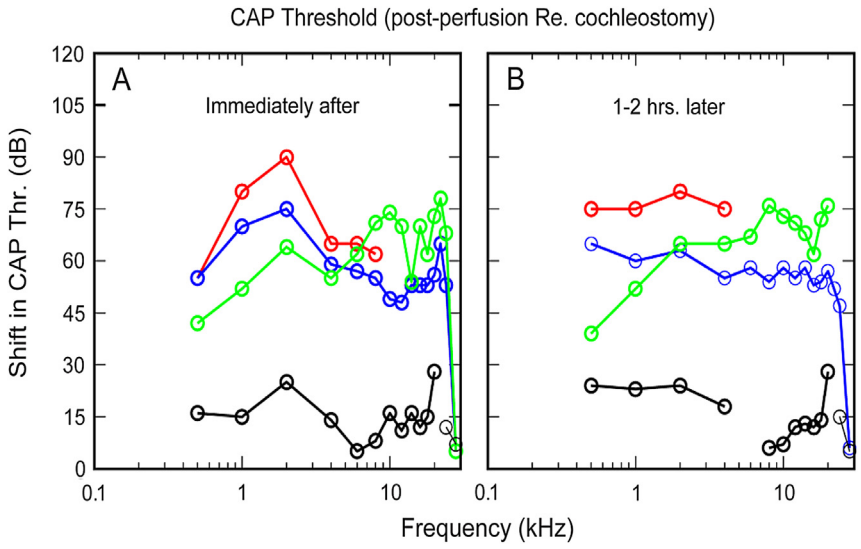

Fig. 7. Change in CAP threshold (re: post-cochleostomy) following 0.5% HA perfusion A: immediately after perfusion and B: ~2 h after perfusion. Each color represents the data from one gerbil. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

HA at the flow rates used might have caused mechanical trauma of a permanent nature as discussed further below.

Fig. 8 shows an example of individual CAP waveforms for 4 kHz frequency, for baseline condition (Fig. 8A) and immediately after HA perfusion (Fig. 8B). This example is a representative of the family of CAP waveforms obtained from HA-perfused cochleae. In the baseline condition, the CAP maximum waveform peak grew and the latency of the peak decreased with increasing sound level. First CAP peak latency decreased gradually by 560 ms from 24 dB SPL to 54 dB SPL in the baseline condition. In contrast, for the post HA-perfusion condition, the first CAP peak latency decreased by 320 ms from 110 dB SPL to 130 dB SPL and the latency changed very little after the first two sound levels. It is possible that the small latency change in the post-perfusion condition was due to the very

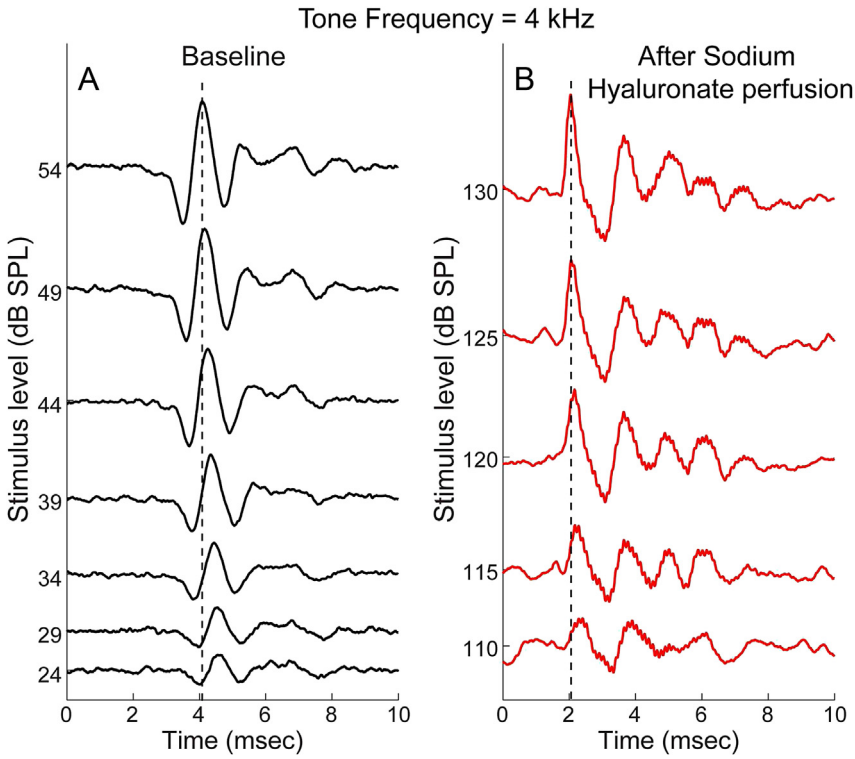

Fig. 8. Individual CAP waveforms from one gerbil before (A) and after HA perfusion (B). Sound levels are shown on *y*-axis. The dashed vertical lines are included to assist in evaluating the SPL-dependent delay.

high sound levels at which the responses were observed. However, the first peak latency at the lowest sound level observed in the post-perfusion case was very short (~2.5 ms) for the 4 kHz region and matches more closely to the auditory-nerve fiber latencies observed following sensorineural hearing loss (e.g., Scheidt et al., 2010). These results suggest a damaged or abnormal mechanism of neural excitation following the HA-perfusion, which is discussed further below.

4. Discussion

4.1. New perfusion-based insertion method minimized histologically-evident intracochlear trauma and resulted in deep insertion

Here we have reported a successful method for deep insertion without overt tissue damage (Fig. 4). What is still unknown is what modifications are needed to make the method truly non-damaging. This is a progress report on a promising, but not yet proven, advance in cochlear implantation, consisting of a relatively simple, fluid-assisted electrode insertion with potential for automation. The method relies on the flow of a viscous fluid through the cochlea; because the implant is insulated from the delicate cochlear structures by a lubricating fluid, it is less likely to exert damaging force on these structures. The method could easily be modified to control the insertion depth. The implant would be marked to the desired length (or insertion depth) and flow stopped to stop the implant from advancing further. Alternatively, the implant could be mechanically stopped at the pre-set insertion depth that can be determined either by measuring acoustically evoked potentials in the round window or by measuring the electrocochleograph (Harris et al., 2011; Choudhury et al., 2012).

The physical properties of the cochlear implants currently used in clinical practice certainly play a role in causing intra-cochlear trauma. For example, stiffer and pre-curved arrays are associated with larger incidences of basilar membrane perforations (e.g., Wardrop et al., 2005a) and can potentially cause osseous spiral lamina fracture (Briggs et al., 2001). In contrast, flexible straight arrays are thought to be less traumatic (Glueckert et al., 2005). However, manual insertion technique places constraints on the flexibility of electrode arrays because if the electrodes are very flexible they tend to vibrate and to respond to forces of surface tension, making it difficult to guide the implant into the cochleostomy or round window. During the insertion, a very flexible electrode being pushed from the back is also susceptible to buckling. Our proposed method is well suited to work with flexible electrodes – the more flexible the better – a property that in itself can minimize the trauma.

Performing a cochleostomy is a standard technique well known to many surgeons and implemented more widely compared to RW insertion. However, even within the group of surgeons favoring the standard cochleostomy approach, there appears to be a lack of consensus regarding the location of the cochleostomy best suited to minimize trauma (Briggs et al., 2005; Adunka and Buchman, 2007; Friedland and Runge-Samuelson, 2009). Initially RW based insertion was rejected due to anatomical constraints of the hook region of the human cochlea (Lehnhardt, 1993). However, recently RW based insertion has been shown to be more successful in minimizing trauma and hearing preservation (e.g., Skarzynski et al., 2007). The proposed method standardizes the insertion technique: automated RW insertion and more uniform insertion depth across subjects. This method requires a cochleostomy to be made in the basal SV, but this is for fluid release and can be relatively small, and placed for minimal potential trauma.

Benefits of deeper insertion have long been debated. Two major arguments in favor of deep insertion are (1) stimulation of surviving dendrites with low current leading to more selective stimulation and wider dynamic range (Briaire and Frijns, 2006) and (2) significant perceptual benefit of receiving low pitch information (Deman et al., 2004). In contrast, many studies have argued against the deeper insertion as (1) it results in significant trauma in the base as well as in the apex that offsets the potential gain of deeper insertion (Ariyasu et al., 1989; Adunka and Kiefer, 2006), (2) survival of SG bodies is considerably higher than their dendritic peripheral processes, diminishing the advantage of a deep insertion and (3) studies looking into perceptual benefits of apical insertion have yielded mixed results (reviewed by Boyd, 2011). It is reasonable to say that a lack of a safe insertion method to minimize insertion trauma while achieving consistent insertion depths across subjects poses a major limitation in fully exploring the benefits of apical insertion. The majority of the electrode insertions do not go past the first basal turn. Even the deepest insertions reported primarily with MED-EL flex electrodes do not span the full extent of SGC cell bodies in terms of the angular distance (Stakhovskaya et al., 2007; Boyd, 2011). The proposed method achieves the deeper insertion to fully cover the angular distance of SGC bodies while minimizing trauma to basal and apical structures. Hence, the new technique can truly help us to fully explore the benefits of apical insertion.

4.2. Limitations of the proposed method and further challenges

We did not see evidence of hearing preservation following HA perfusion (Fig. 5). However, the results presented were all from acute studies and a chronic effect of HA perfusion remains to be seen. Round window application of HA in rats (Laurent et al., 1992) resulted in immediate drop in ABR thresholds but the thresholds returned to normal two months postoperatively. HA used for stapedectomy in humans did not result in any sensorineural hearing loss when the gel came in contact with the perilymph (Angeli, 2006). The general consensus among surgeons seems to be in favor of the use of HA during cochlear implant surgeries (reviewed by Friedland and Runge-Samuelson, 2009). However, none of these studies perfused the whole cochlea with HA. The only study that injected rat cochleae with HA (Roland et al., 1995) observed severe sensorineural hearing loss but with no effect of HA on SG cell morphology, SGC count or axonal survival. This study also observed profound hearing loss with Glycerin. The sensorineural hearing loss observed by Roland et al. (1995) might be related to significant pressure buildup within the cochlea and increased fluid volume during the injection procedure since no outlet was provided for the injected solutions. Salt et al. (2009) reported large threshold shifts following HA injections in the apex of the guinea pig cochleae. However, CAP thresholds returned to baseline following the removal of the gel. There was no outlet provided for the injected HA. Their study differed from the present study in terms of the volume injected (2 μL in guinea pigs vs. more than 10 μL in our gerbils) and the flow rate used (0.1–20 nL/min in guinea pigs vs. 24 μL/min). Thus, the present study of HA *perfusion* cannot be directly compared with the previous studies of HA *injection*. The high flow rate used in the present study might have resulted in the high CAP thresholds that we observed post-perfusion. When the same flow rates were used with AP (with the viscosity of water, ~1000 times less than 0.5% HA), near-normal CAP responses were observed (Fig. 6).

We observed mild-moderate threshold elevation in two of the three animals perfused with AP (Fig. 6). However, the threshold elevation was much less at low frequencies following AP perfusion than that following HA perfusion (compare Figs. 5D to 6D). These results suggest that the perfusion method itself does not produce the threshold elevation following HA perfusion. Many previous studies of cochlear mechanics have used cochlear perfusion without damage due to the perfusion (Nuttall et al., 1982). The green curve of Fig. 6 is what is possible and based on the literature, should be regularly attainable for perfusion with AP. Chronically it may be possible that CAP thresholds return to baseline making the proposed perfusion based insertion method a viable technique.

Although we did not do chronic HA perfusions, we waited for 1–2 h following the perfusion anticipating that the cochlea will rid itself off of HA and replace it with perilymph. However, even after 1–2 h and despite the re-perfusion with AP, CAP thresholds did not return to the post-cochleostomy level (Fig. 7). We speculate that the viscous nature of HA might have altered basic cochlear traveling wave mechanics. The presence of fluid more viscous than natural perilymph may lead to excitation via a non-traveling, "fast" wave mode (Huang and Olson, 2011). Such excitation may cause the first-peak latency in CAP waveforms to be both reduced and relatively independent of the sound level presented, as seen in Fig 8. Thus, based on the data we have, adverse mechanical effects of HA on cochlear mechanics are present, at least short-term. It is also possible that the flow-rates used during perfusion combined with the viscous nature of the carrier fluid resulted in permanent mechanical trauma to Reissner's membrane due to the high shear stress caused by the viscous HA. Shear stress is proportional to both viscosity and flow rate. However, if the viscosity and/or flow rate are substantially reduced the perfusion insertion technique is less successful. On the other hand, we have made improvements in perfusion-insertion with more dilute (less viscous) HA by treating the surface of the implant so that it is more hydrophilic. This is an area for future work.

The proposed method requires a cochleostomy to be performed in SV to provide an outlet for HA and to set-up a unidirectional flow. While this can be considered as a formidable challenge, the size of the cochleostomy required is very small, since it is only needed for fluid release. Such a small hole made using soft surgery techniques may not pose a major threat to the long-term goal of hearing preservation. Another limitation of the method is that at present there is no control over electrode placement relative to the modiolus. Finally, connecting the electrode array to the preceding circuitry following insertion is a non-trivial challenge. We are currently working on modifying the design of the insertion tool such that a connector will not be required between the electrode array and the receiver-stimulator circuit.

In summary, we have presented proof-of-concept results from an ongoing project to develop a reliable non-traumatic technique for deep CI electrode insertions. Deep insertions were achieved and histologically the implanted cochleae appeared undamaged. However, a number of challenges remain and the technique requires further research and development before its clinically viability is known.

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