Published in final edited form as:

Otol Neurotol. 2014 March ; 35(3): 519–525. doi:10.1097/MAO.0b013e31829bdf2b.

Electrophysiologic Consequences of Flexible Electrode Insertions in Gerbils with Noise Induced Hearing Loss

Baishakhi Choudhury, MD, **Oliver F. Adunka, MD, FACS**, **Omar Awan, BS**, **John Maxwell Pike, BA**, **Craig A. Buchman, MD, FACS**, and **Douglas C. Fitzpatrick, PhD**

Department of Otolaryngology/Head and Neck Surgery, The University of North Carolina at Chapel Hill; Chapel Hill North Carolina, USA

Abstract

Hypothesis—Flexible electrode interaction with intracochlear structures in a noise-damaged region of the cochlea can lead to measureable electrophysiologic changes.

Background—An emerging goal in cochlear implantation is preservation of residual hearing subsequently allowing for combined electric and acoustic stimulation (EAS). However, residual hearing is at least partially lost in most patients as a result of electrode insertion. A gerbil model was used to examine changes to acoustically evoked cochlear potentials during simulated cochlear implantation.

Methods—Gerbils were partially deafened by noise exposure to mimic residual hearing in human cochlear implant candidates. After one month, round window (RW) and intracochlear recordings during flexible electrode insertion were made in response to 1 kHz tone burst stimuli at 80 dB SPL. After the insertion the cochleas were histologically examined for hair cell loss due to the noise exposure and trauma due to the electrode insertion.

Results—Anatomical damage from the flexible electrode was not observable in most cases. However, insertions caused response declines that were on average greater than the controls, although some losses were similar to the controls. The CM was more sensitive than the CAP for detecting cochlear disturbance.

Conclusions—Because response reductions occurred in the absence of anatomical damage, disturbances in the fluid at the base appear to affect responses from the apex. The losses were less than in previous experiments where the basilar membrane was penetrated.

Corresponding Author/Proofs and Reprint Requests: **Oliver F. Adunka, MD, FACS**, Associate Professor, Otology, Neurotology, Skull Base Surgery, Department of Otolaryngology/Head and Neck Surgery, The University of North Carolina at Chapel Hill, 170 Manning Drive, POB, CB 7070, Chapel Hill, NC 27599, Phone: (919) 966-3342, Fax: (919) 966-7941, ofa@med.unc.edu.

Disclosures:

Douglas C. Fitzpatrick: Contractual research support from Advanced Bionics, Cochlear Corporation, and MED-EL Corporation. Craig A. Buchman: Contractual research support from Cochlear Corporation and MED-EL Corporation; research grant support from the NIH-NIDCD, unpaid consultant for Advanced Bionics, Cochlear Corporation, MED-EL Corporation, and Anspach Corporation. Oliver F Adunka: Contractual research support from Advanced Bionics, Cochlear Corporation, and MED-EL Corporation.

Keywords

Cochlear implantation; Cochlear electrophysiology; Hearing preservation; Compound action potential; Cochlear microphonic; Electrocochleography

INTRODUCTION

An emerging goal during cochlear implantation (CI) is to preserve residual hearing and to provide a combination of acoustic and electric stimuli to the same ear; a paradigm termed Hybrid cochlear implantation[1], electric-acoustic stimulation (EAS)[2,3], or partial deafness cochlear implantation (PDCI)[4]. Such a stimulation mode obviously relies on functional hearing preservation, which in turn has been linked to non-traumatic electrode insertions. However, even patients with little to no residual hearing can benefit from minimally traumatic electrode insertions and many studies have shown that less traumatic insertions are correlated to improved performance measured postoperatively[1,5,6].

Currently the electrode array is placed in essentially a blind manner, and the surgeon has little feedback regarding electrode positioning within the cochlea. Transition of the electrode from scala tympani to scala vestibuli can have a severe effect on speech outcomes with the implant[7,8]. Such trauma would be expected to severely disrupt residual hearing as well. Although methods to provide direct visualization during the insertion process are being investigated[9], none exist for clinical use today. An alternative approach is to monitor the status of residual hearing during insertion. This study is part of a series to investigate physiological markers of cochlear trauma in an animal model. The work is timely because monitoring attempts are being performed in human implant patients[10,11], and reliable markers identified in animals may prove useful. In addition, recordings at the round window in human subjects show that almost all patients have responses to auditory stimulation[12]. Consequently, the intraoperative recording approach for monitoring implant insertion can be applicable to the full range of implant candidates, not just those where hearing preservation is the goal.

In our previous studies, we have used the gerbil to study electrophysiological responses from the cochlea to auditory stimulation during simulated electrode insertions. Perturbations of the basilar membrane with rigid electrodes to produce trauma have been made in gerbils with normal hearing[13–15] and animals with noise induced hearing loss (NIHL)[16]. These experiments were done with rigid electrodes directed though the round window toward the basilar membrane. In the normal-hearing animals, a consistent and sensitive marker for trauma was a reduction in the cochlear microphonic (CM) in response to a suprathreshold tonal stimulus. This response reduction was a more sensitive and reliable marker than a change in threshold. Changes in the CM, a monitor of hair cell response, were observed with less trauma than was the case for the compound action potential (CAP), a measure of response from the auditory nerve. The noise damaged model is useful because it mimics the hearing condition of a human implant candidate. In the noise-damaged animals, the CM remained a more sensitive marker of cochlear trauma than the CAP. However, reversible damage was not observed. Insertions with a flexible electrode mimicking a clinic implant

have been done in normal-hearing animals[17]. In that condition, the responses to different frequencies showed complex changes as the electrode longitudinally traversed the basal turn. The experiments described here used a flexible electrode in noise-damaged animals, so that both the electrode and hearing condition are most relevant to the clinical condition.

MATERIALS AND METHODS

The following is a brief overview of the study: 1) Gerbils were noise-exposed to produce hearing loss comparable to those of EAS candidates with residual low frequency hearing. 2) One month after noise exposure, a flexible electrode array was inserted through the round window in a stepwise fashion while periodic electrocochleography measures were made to a 1 kHz tone burst stimulus. 3) The cochleae were histologically processed to identify loss of hair cells due to noise exposure and cochlear trauma caused by electrode insertion.

Animals

The Mongolian gerbil *(Meriones unguiculatus)* was used because it has a low frequency hearing range similar to humans, and because the cochlea is readily accessible. All animals were handled and housed according to the standards described by the National Institutes of Health Committee on Care and Use of Laboratory Animals. The experimental protocols were approved by the Institutional Animal Care and Use Committee at the study institution.

Noise Exposure

The noise exposure has been previously used and shown to produce highly reproducible damage to cochlear structures and function[16,18]. Briefly, the anesthetized gerbil (Nembutal 60 mg/kg) was placed in a single-walled sound-attenuated chamber (Industrial Acoustics, NY) under a loud speaker (Selenium, Nova Santa Rita/RS Brazil, Model D3300Ti). High-pass noise with a cut-off frequency of 4 kHz was presented at 122 dB sound pressure level (SPL, re 20 μPascal) for four hours. The sound level was monitored throughout the exposure period with a ¼” Bruel and Kjaer (Naerum, Denmark) microphone and did not vary more than 1 dB. A 4 kHz high-pass cut-off was chosen since it corresponds to the 1–1.5 kHz frequency range in the human as both frequencies are slightly less than 50% distance from the apex. Current candidacy criteria for cochlear implants require that the patient has severe-to-profound sensorineural hearing loss for frequencies above 1.5 kHz, but candidates can have a mild-to-moderate hearing loss below 1.5 kHz. After noise exposure, a period of four weeks was allowed for cochlear damage to stabilize.

Acoustic Stimulation for Electrocochleography

Electrical signals were generated and delivered to a well-shielded loudspeaker (Beyer DT-48, Farmingdale, NY, USA) using custom software, a National Instruments input/output board (model 6250E, Austin, TX, USA), and a Tucker-Davis headphone buffer (model HB7, Alachua, FL, USA). The stimuli were tone bursts with a 10 ms plateau and 2 ms rise/fall times, and a 30 ms inter-stimulus interval. The speaker was placed 15 cm from the animal’s tympanic membrane. Calibration was performed via a ¼ inch microphone placed at the position of the animal’s head (B&K, Nærum, Denmark).

Surgery and Electrocochleography

The round window (RW) was exposed via a craniotomy into the auditory bulla. The recording electrode was attached to a hydraulic micromanipulator and placed against the intact RW membrane. The electrodes were scaled versions of human electrode arrays provided by MED-EL Corporation (Innsbruck, Austria). They had one or two ball-like electrode contacts encased in a 200 μm diameter silastic carrier (see Fig. 2 in DeMason et al[17]). The recording was differential and monopolar, with the electrode connected to the positive input of a preamplifier (Grass Instruments, model P15D, West Warwick, RI). A wire clipped to the neck musculature served as the negative, and the system ground was connected to the animal's tail.

The electrode was inserted through a small incision made in the lateral aspect of the RW membrane. It was advanced so that the distal most contact (used for recording) was positioned immediately past the RW within scala tympani. The 1 kHz tone was presented with three sets of 100 repetitions each. Amplification was 100x and filters were bandpass from 10–50,000 Hz. The output led to the outside of the sound booth where there was additional amplification (10x) and filtering (10 –50,000 Hz). The waveform was then digitized (200 kHz sampling rate) and averaged.

The electrode was then advanced in 100 μm increments along scala tympani using the hydraulic micromanipulator, with the recordings repeated at each step. The electrode was advanced until abrupt or substantial reductions in the CM and/or CAP consistent with intracochlear damage were observed, or the silastic carrier began to buckle indicating that the narrowing of scala tympani at the end of the basal turn prevented further advancement. Thereafter, the electrode was retracted back to the RW to see if physiologic changes noted during the insertion process were permanent. Once complete, cochleae were harvested for histology.

Physiological Data Analysis

The CM signal was analyzed from the last 7 ms of the 10 ms plateau. Its magnitude at the stimulus frequency was determined from the amplitude component of a fast-Fourier transform (FFT) of the response. The CAP was measured as the largest peak-to-peak excursion within 6 ms after stimulus onset.

Histology

After electrophysiological recordings were completed on each NIHL gerbil, the animal was sacrificed and the cochleae were removed en block and preserved in fixative (4% paraformaldehyde). The samples were decalcified and bone was removed for improved visualization of cochlear structures. In the cochlea contralateral to the electrode insertion, the BM was further dissected so that it could be flattened, stained (iron hematoxilin), mounted and coverslipped. Hair cell losses were counted in 250 μm increments using a Zeiss Axioscope with 40x objective (Carl Zeiss Inc, Thornwood, NY). In the cochlea where the electrode was inserted, the specimen was stained with toluidine blue and viewed and photographed at 50X using a Wild M50 dissecting microscope (Leica Inc., Wetzler, Germany).

RESULTS

Table 1 lists all the animals included in the study with a summary of their respective anatomic and physiologic findings.

Anatomy

All cases had changes to the cellular structure of the organ of Corti at the base of the cochlea indicative of hair cell/supporting cell damage as a result of noise exposure, while in the apex it was normal in architecture. Hair cell counts (Fig 1) were consistent with previous findings using the same the noise exposure parameters[16,18].

Figure 2A is an example of the mechanical trauma created by the flexible electrode as it traverses scala tympani. The disruption to the basilar membrane can be seen more clearly in the more magnified image in Fig 2B. However in other cases no gross damage under the dissecting microscope was noted (Fig 2C and Table 1). Though no mechanical damage from the electrode could be visualized, the noise exposure damage to the base of the basilar membrane is apparent in Fig 2C. A more magnified area of the transition zone where normal architecture of the basilar membrane with ordered hair cells meets an area with clearly effaced architecture is depicted in Fig 2D.

Physiology

At the end of an insertion there were variable degrees of change in the response compared to the beginning. In Fig. 3, each row compares the first and last recording for a different gerbil. The left column is the time waveform of the response at the beginning, and middle column is the response at the end of the insertion. The right column is the spectrum of the CM with the two responses superimposed. The top row is a case where the change in response was quite small. The middle row is a case where the response loss was moderate, and the bottom row is a case where the response loss was large.

The distribution of these responses is shown in Fig. 4. For comparative purposes, we also show the results from a previously published study where a rigid electrode was used to penetrate the basilar membrane in similarly noise-damaged animals[16]. Fig 4A shows the results from each case, and Fig. 4B shows a box and whisker plot of the same data. The response loss from the flexible electrode was much less than with the rigid electrode. This result is consistent with the anatomical results, since with the rigid electrode the basilar membrane was always penetrated resulting in considerable histological damage, while with the flexible electrode cochlear trauma was small or absent. The next feature to note is that there were physiological losses with the flexible electrode greater than in controls, despite the relative absence of histological damage.

Using a one-way ANOVA to analyze the data in Fig. 4, there was a main effect of group ($F=17.8$, $df=3$, $p<0.001$). Using t-tests for individual comparisons the difference between the rigid and flexible electrode was significant (one-tailed, $t=4.98$, $df=12.4$, $p<0.001$) as was the difference between the experimental cases with the flexible electrode and controls (one-tailed, $t=2.73$, $df=13.9$, $p<0.01$).

In addition to the variability with endpoints across cases, there was also variability during the course of the insertion. Figure 5 shows examples of recording tracks for three gerbils (A–C). For each gerbil, the top panel is the depth of insertion, and the bottom panel is the response normalized to the start of the track. The CM is shown in filled circles and the CAP in open circles. For the first gerbil (Fig. 5A) there was a slight increase in response through most of the track, followed by a return to baseline when the electrode was withdrawn to the round window. This pattern suggests that no trauma occurred during the insertion, but that as the electrode traversed the basal turn it was closer to or had a better orientation to the generators of the responses. In the second gerbil (Fig. 5B) the CM declined abruptly at 1.1 mm from the round window, and did not recover when the electrode was returned to the round window. A drop in the CAP did not occur until later. The abrupt drop in the CM suggested that trauma had occurred so the electrode was not further advanced. However no trauma was apparent in the histology (Table 1). For the third gerbil, there was a similar abrupt drop as in the previous case, again with the CM leading the CAP. In this case there was noticeable trauma to the basilar membrane consisting of a tenting process when viewed from above, as in the case in Fig. 2A and C. The location of the damage (Table 1) corresponds to the depth of the drop in response. This represents the only case with a correlation between physiology and anatomy.

DISCUSSION

When a flexible electrode was inserted into the cochlea of a gerbil with noise induced hearing loss, one outcome observed was that the electrode could be advanced to the end of the basal turn with little or no physiologic or anatomic effect that was different from controls. This outcome indicates that the flexible electrode can be inserted atraumatically without causing a decline in cochlear function. The second outcome was a decline in the CM and CAP that could be abrupt. A subset of this second group (3 cases) had visible histologic damage.

The physiological marker for cochlear trauma was the response to a suprathreshold, 1 kHz tone. This stimulus was used because in the noise-damaged animals it was more sensitive and reliable than frequencies of 2–16 kHz used with normal hearing animals. As seen in our previous studies with this hearing condition[16,18], a response to a 1 kHz tone was present in each animal studied, despite the fact that the recordings were at the round window and the response must have been generated from apical hair cells and nerve fibers. This result is comparable to recordings from human implant subjects, where responses to low frequencies are recordable from the round window in almost all subjects[10–12].

As in our previous studies, a reduction in the CM was typically observed earlier in the insertion than the CAP. We have consistently seen that reductions in the CM represent the most sensitive marker of cochlear physiological change, irrespective of the hearing condition or type of electrode used. This difference is expected because at the suprathreshold intensities used the CM is in a linear range of response, while the CAP is saturated[13].

Anatomical trauma due to electrode insertion was similar in size and location to previous findings by DeMason et al[17] where flexible electrodes were used for cochlear implant simulations in normal-hearing animals. In that report there were also numerous cases with CM and CAP response reductions without obvious histologic damage. The physiologic decline was attributed to reversible contact with functional hair cells in the basal turn. However, even in the noise damaged cases reported here there were obvious cases of decline in the CM, even though the hair cells responsible for the response were remote from the electrode. The reasons for this result are not entirely clear. Declines occurred even in the control animals where the electrode was inserted through the round window but not advanced. This result indicates that pressure disturbances of the fluid environment may be enough to introduce a physiological change. Further perturbations of the fluid would be expected to occur with further insertion, which may be the cause of the reductions observed.

The flexible electrode used in this study and the previous study was never seen to travel through the basal membrane. Anatomical damage in most cases was absent and was never large. This result is in contrast to clinical cases with conventional implantations where penetration through the basilar membrane may be common[7,8]. Penetration of the basilar membrane in the noise-damaged animals was addressed in our previous study with a rigid electrode, where it did result in large response reductions[16]. Here, the flexible electrode more closely resembled the soft electrode designs used in hearing preservation surgeries. The results indicate that it is possible to insert these electrodes at least through the basal turn with little anatomical effect and in most cases modest physiological effect.

The implication of the results for monitoring in human implant subjects is that relatively small losses of response may not indicate cochlear trauma, but may instead be indicative of fluid disturbances. In contrast, large losses are likely to be irreversible, and thus preservation of hearing is unlikely. In this case it might be best to proceed to a full insertion and not expect success with EAS.

REFERENCES

1. Gantz BJ, Hansen MR, Turner CW, Oleson JJ, Reiss LA, Parkinson AJ. Hybrid 10 clinical trial: preliminary results. Audiol Neurootol. 2009; 14(Suppl 1):32–38. [PubMed: 19390173]
2. von Ilberg C, Kiefer J, Tillein J, et al. Electric-acoustic stimulation of the auditory system. New technology for severe hearing loss. ORL J Otorhinolaryngol Relat Spec. 1999; 61:334–340. [PubMed: 10545807]
3. Gstoettner W, Kiefer J, Baumgartner WD, Pok S, Peters S, Adunka O. Hearing preservation in cochlear implantation for electric acoustic stimulation. Acta Otolaryngol. 2004; 124:348–352. [PubMed: 15224851]
4. Skarzynski H, Lorens A, Piotrowska A. A new method of partial deafness treatment. Med Sci Monit. 2003; 9:CS20–CS24. [PubMed: 12709676]
5. Gantz BJ, Turner CW. Combining acoustic and electrical hearing. Laryngoscope. 2003; 113:1726–1730. [PubMed: 14520097]
6. Gstoettner WK, Van De Heyning P, O'Connor AF, et al. Electric acoustic stimulation of the auditory system: results of a multi-centre investigation. Acta Otolaryngol. 2008:1–8.
7. Finley CC, Holden TA, Holden LK, et al. Role of electrode placement as a contributor to variability in cochlear implant outcomes. Otol Neurotol. 2008; 29:920–928. [PubMed: 18667935]

8. Skinner MW, Holden TA, Whiting BR, et al. In vivo estimates of the position of advanced bionics electrode arrays in the human cochlea. Ann Otol Rhinol Laryngol Suppl. 2007; 197:2–24. [PubMed: 17542465]

9. Roland JT Jr, Fishman AJ, Alexiades G, Cohen NL. Electrode to modiolus proximity: a fluoroscopic and histologic analysis. Am J Otol. 2000; 21:218–225. [PubMed: 10733187]

10. Radeloff A, Shehata-Dieler W, Scherzed A, et al. Intraoperative monitoring using cochlear microphonics in cochlear implant patients with residual hearing. Otol Neurotol. 2012; 33:348–354. [PubMed: 22377649]

11. Mandala M, Colletti L, Tonoli G, Colletti V. Electrocochleography during cochlear implantation for hearing preservation. Otolaryngol Head Neck Surg. 2012; 146:774–781. [PubMed: 22291043]

12. Choudhury B, Fitzpatrick DC, Buchman CA, et al. Intraoperative round window recordings to acoustic stimuli from cochlear implant patients. Otol Neurotol. 2012; 33:1507–1515. [PubMed: 23047261]

13. Adunka OF, Mlot S, Suberman TA, et al. Intracochlear recordings of electrophysiological parameters indicating cochlear damage. Otol Neurotol. 2010; 31:1233–1241. [PubMed: 20818290]

14. Campbell AP, Suberman TA, Buchman CA, Fitzpatrick DC, Adunka OF. Flexible cochlear microendoscopy in the gerbil. Laryngoscope. 2010 accepted for publication.

15. Campbell AP, Suberman TA, Buchman CA, Fitzpatrick DC, Adunka OF. Correlation of early auditory potentials and intracochlear electrode insertion properties - an animal model featuring near real-time monitoring. 2010 submitted.

16. Choudhury B, Adunka OF, Demason CE, Ahmad FI, Buchman CA, Fitzpatrick DC. Detection of intracochlear damage with cochlear implantation in a gerbil model of hearing loss. Otol Neurotol. 2011; 32:1370–1378. [PubMed: 21921858]

17. DeMason C, Choudhury B, Ahmad F, et al. Electrophysiological properties of cochlear implantation in the gerbil using a flexible array. Ear Hear. 2012; 33:534–542. [PubMed: 22436408]

18. Suberman TA, Campbell AP, Adunka OF, Buchman CA, Roche JP, Fitzpatrick DC. A gerbil model of sloping sensorineural hearing loss. Otol Neurotol. 2011; 32:544–552. [PubMed: 21389900]

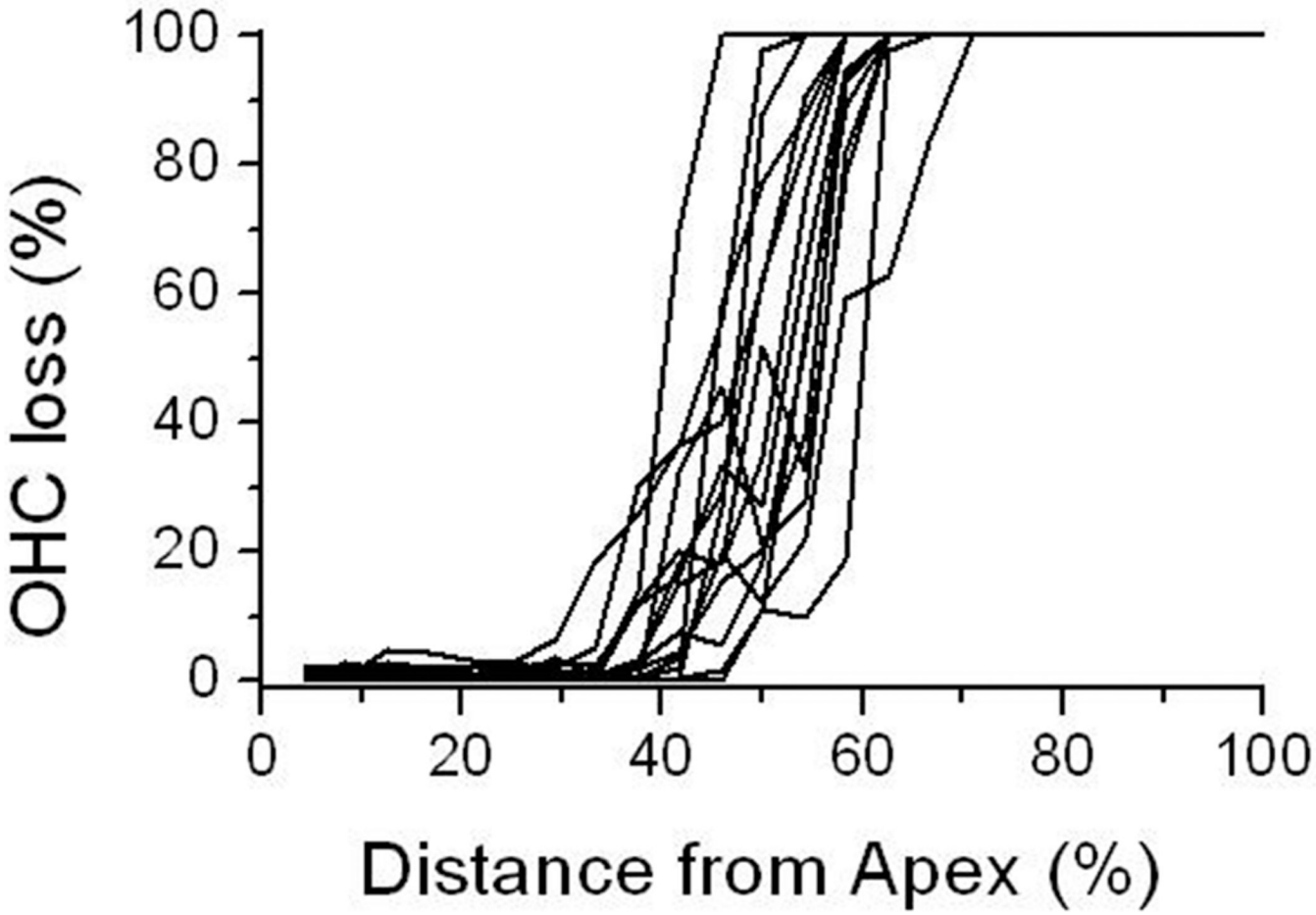

Figure 1.

Percent outer hair cell loss due to noise exposure as a function of distance from the apex. Near the base there was complete loss of outer hair cells, near the midpoint of the cochlea there was a transition zone with some loss of hair cells, and at the apex there was complete preservation of hair cells.

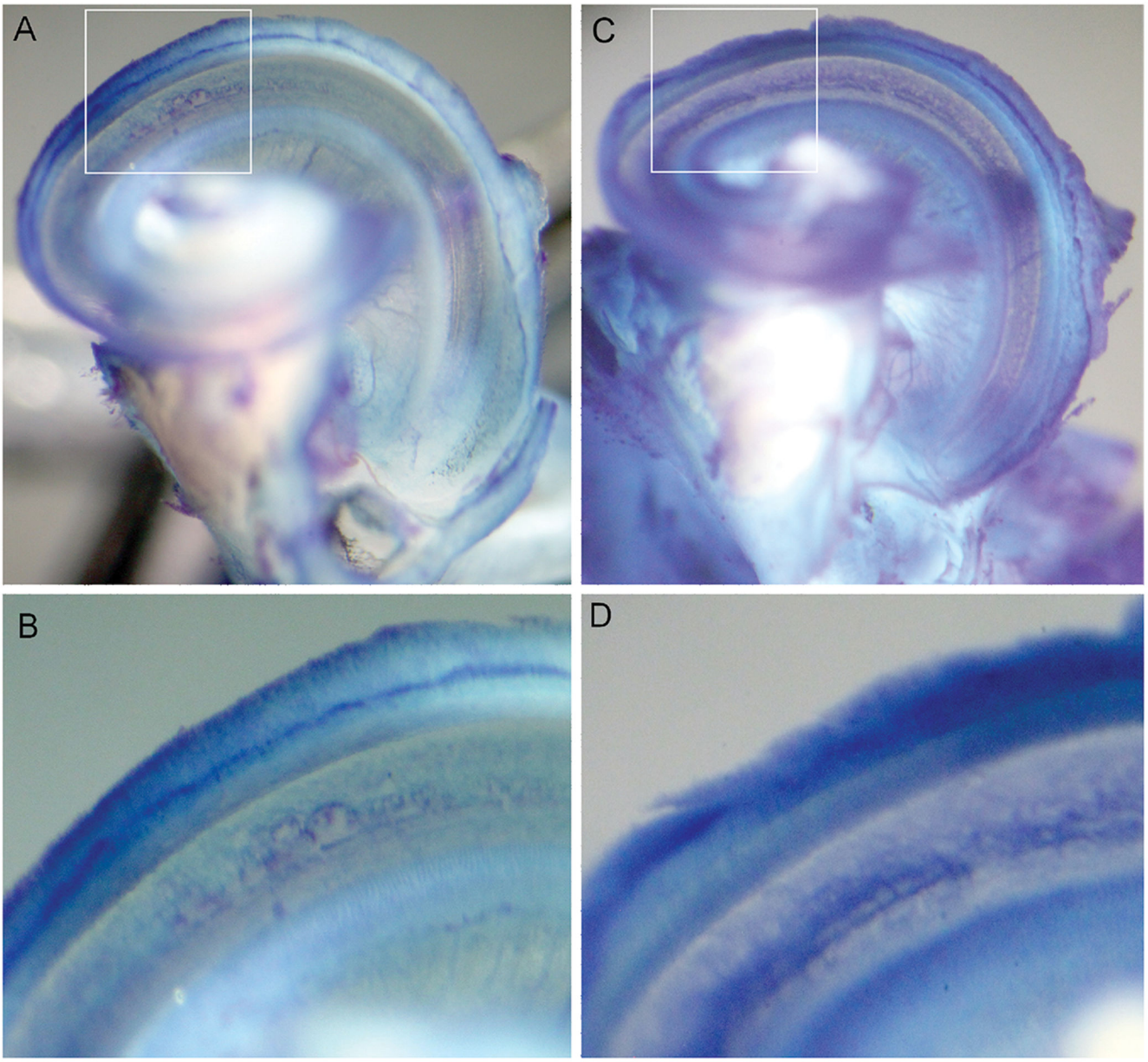

Figure 2.

Examples of histology after noise exposure and flexible electrode insertion. **A and B:** case where damage from the electrode was apparent. **C and D**: case where the electrode was inserted and removed without causing visible trauma.

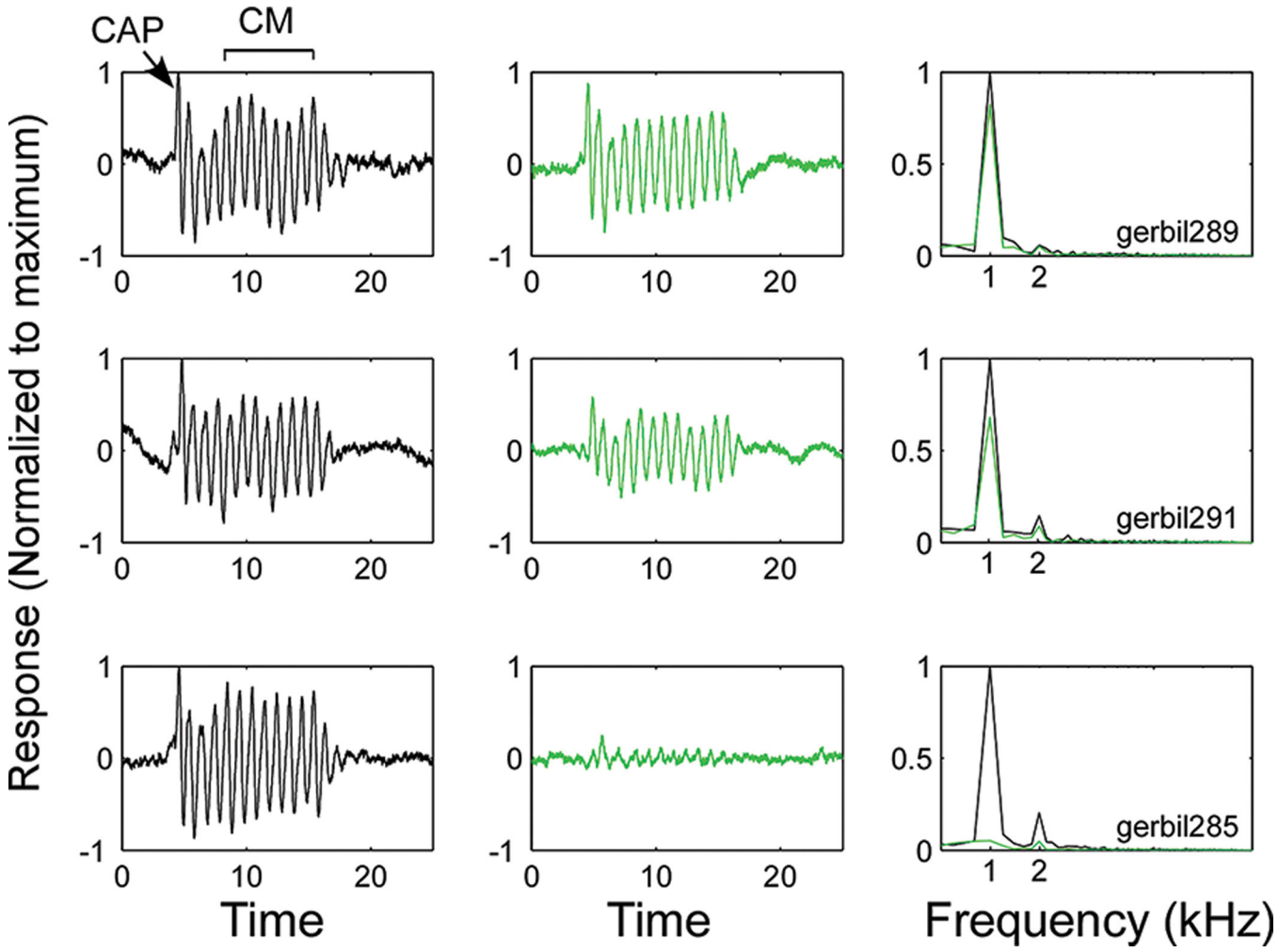

Figure 3.

Comparison of responses at the beginning and end of insertions. Each row is a different gerbil. The left column is the time waveform of the response at the beginning, and the middle column is the waveform at the end of the insertion. The right column is the spectrum of the CM with the two responses superimposed. The top row is a case where the change in response was quite small. The middle row is a case where the response loss was moderate, and the bottom row is a case where the response loss was large.

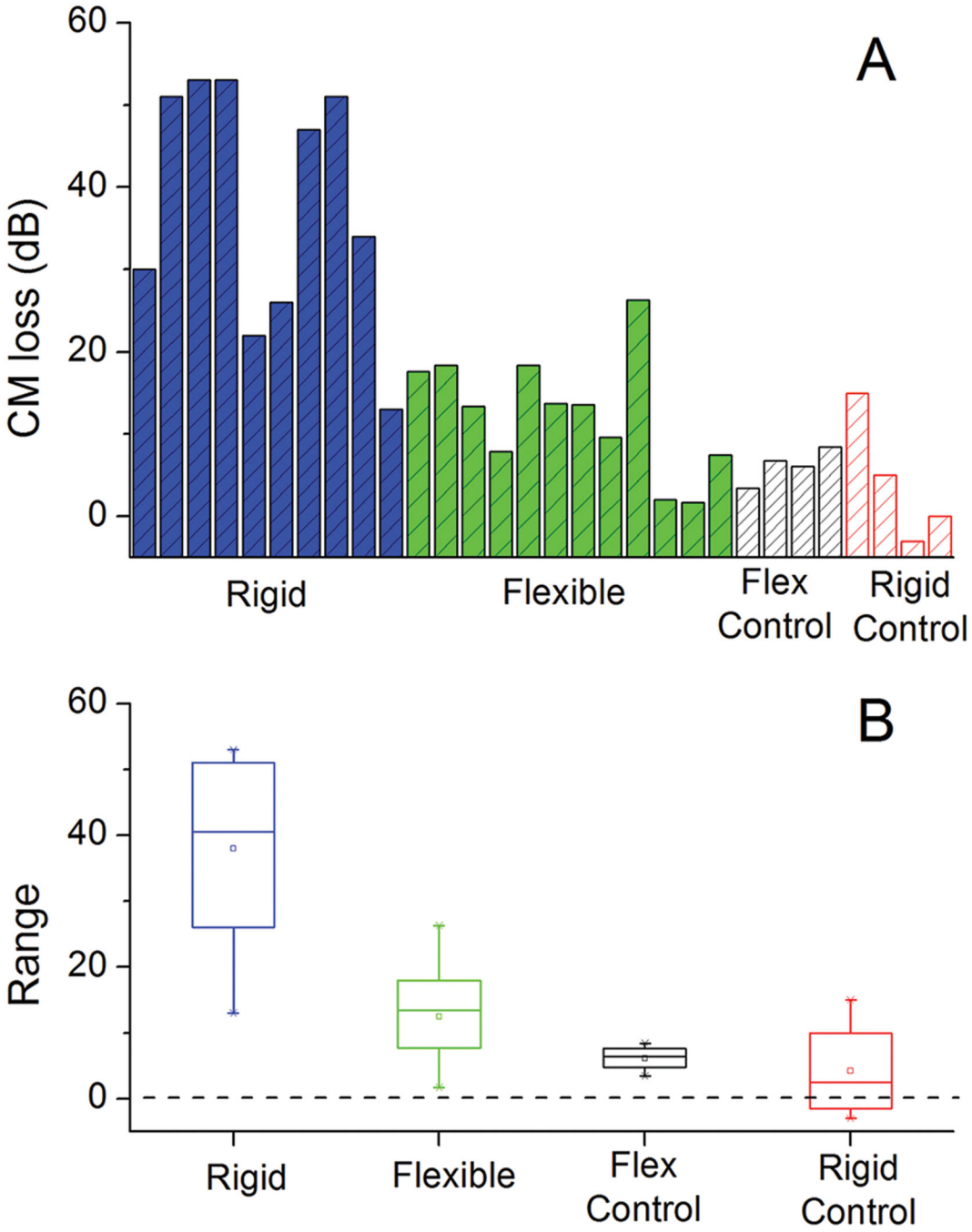

Figure 4.

Summary of the response loss after the insertion. **A:** Each bar is a single case. Data from a previous study using a rigid electrode that penetrated the basilar membrane is shown for comparison[16]. **B:** Same data as in A but shown as a box and whisker format.

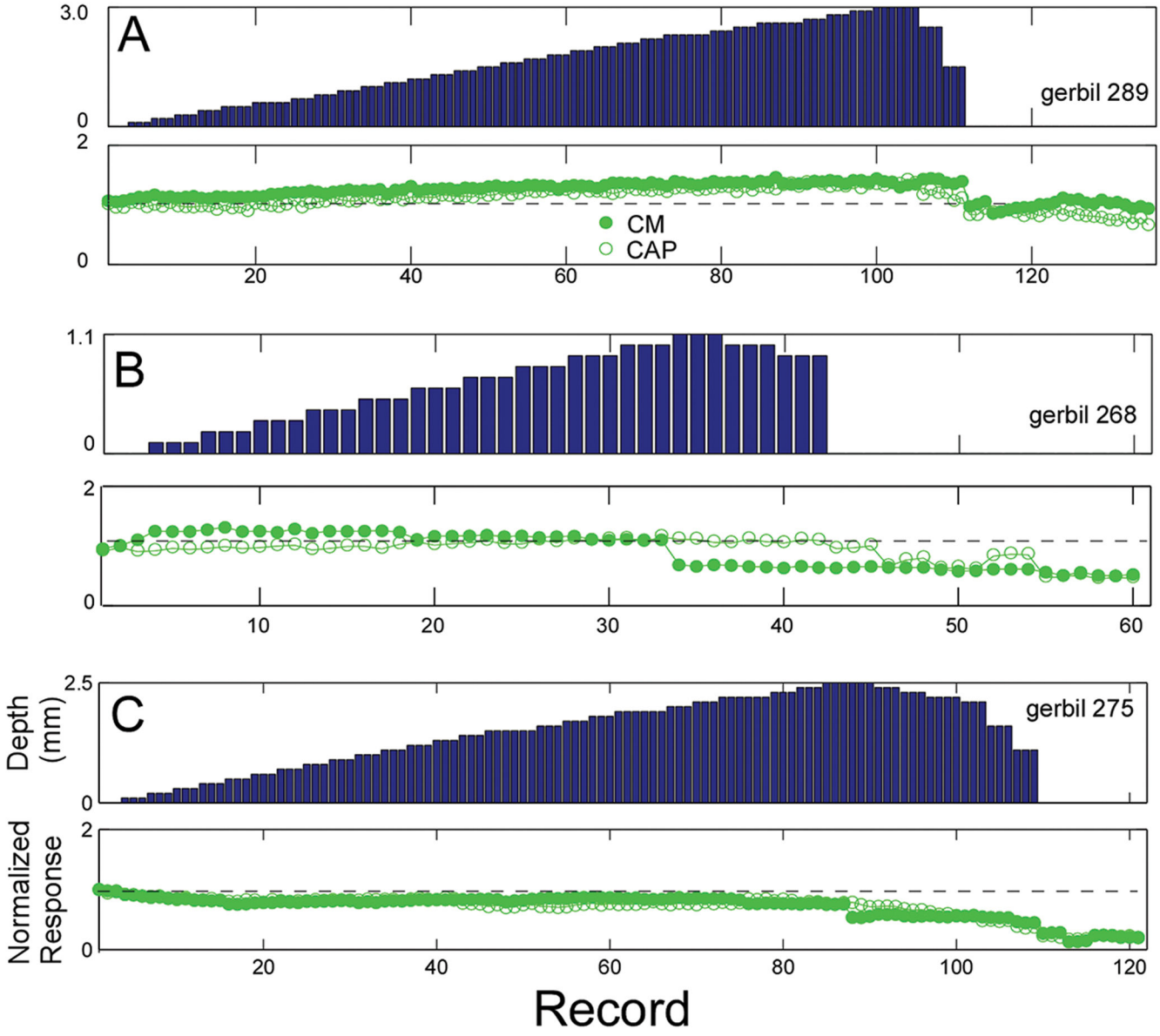

Figure 5.

Examples of responses during the insertion in three animals. For each gerbil, the top panel is the depth of insertion, and the bottom panel is the response normalized to the start of the track. **A:** For this gerbil there was a slight increase in response through most of the track, followed by a return to baseline when the electrode was withdrawn to round window. **B:** For this gerbil, the CM declined abruptly at 1.1 mm from the round window. The CAP did not show as abrupt a decline. Neither response recovered when the electrode was returned to the round window. **C:** For the third gerbil, there was a similar abrupt drop as in the previous case, again with the CM leading the CAP.

Table 1

Summary of animals, procedures, and location and extent of trauma.

Animal #	Max Electrode Insertion Depth	Visible Histologic Damage from Electrode Present?	Size of Damage (mm)	Distance of damage from RW (mm)	Greenwood freq at damage location (kHz)	% CM decline (dB)	% CAP decline (dB)
193	3.8 mm	yes	0.9	1.18	12.4 – 18.6	69.85	150.49
197	3.3 mm	no	n/a	n/a	n/a	67.80	114.02
202	4.1 mm	no	n/a	n/a	n/a	57.00	109.93
262	2.5 mm	no	n/a	n/a	n/a	47.22	30.91
268	1.1 mm	no	n/a	n/a	n/a	98.38	112.94
275	2.5 mm	yes	0.64	2.2	9.5 – 12.7	51.28	72.18
276	1.1 mm	no	n/a	n/a	n/a	59.16	90.43
282	3.0 mm	yes	0.53	0.9	17.9 – 22.7	40.68	41.73
285	0.6 mm	no	n/a	n/a	n/a	93.71	84.26
286	3.0 mm	no	n/a	n/a	n/a	12.83	43.95
289	3.0 mm	no	n/a	n/a	n/a	7.30	13.86
290	3.0 mm	no	n/a	n/a	n/a	33.38	−9.27
291a	0.0 mm	no	n/a	n/a	n/a	13.59	36.88
291b	0.0 mm	no	n/a	n/a	n/a	27.23	38.86
303	0.0 mm	no	n/a	n/a	n/a	20.05	21.96
305	0.0 mm	no	n/a	n/a	n/a	26.95	33.26