

A Soft-Surgery Approach to Minimize Hearing Damage Caused by the Insertion of a Cochlear Implant Electrode: A Guinea Pig Animal Model

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Objective: A “soft surgery” technique was applied, using various types of specifically designed dummy electrodes, to mimic cochlear implantation in a guinea pig model, and the degree of hearing-preservation/cochlear damage was assessed.

Methods: Tricolor guinea pigs were divided into 3 groups: group A were implanted with electrodes without any contacts or wires (soft electrode), group B were implanted with electrodes having a metallic wire inside (stiff electrode), and group C underwent a cochleosotomy procedure without implantation. Compound action potentials, in the range of 4 to 32 kHz, were used to assess electrophysiologic changes in the hearing function presurgery and postsurgery. Data were collected before surgery, at times $t = 0$ (immediately after surgery) and at 3, 7, 14, and 30 days.

Results: At low frequencies (4–8 kHz), an immediate elevation of hearing threshold was observed in all 3 groups. Higher

threshold shifts were more consistent for group B implanted with a stiff electrode, in comparison to the other 2 groups. Animals from group C presented a recovery from hearing loss, starting 3 days after surgery. At high frequencies (16–32 kHz), the elevation of hearing threshold was higher, as compared with the data from the low frequencies. Group C animals presented oscillatory threshold shifts twice, and the recovery to normal threshold values occurred approximately at $t = 14$ days.

Conclusion: The data suggest that cochleosotomy is minimally harmful to the inner ear and that a soft electrode might better preserve the inner ear integrity than a rigid electrode. **Key Words:** Auditory brainstem response—Cochlear implant—Compound action potential—Guinea pig—Residual hearing—Soft surgery.

Otol Neurotol 35:1440–1445, 2014.

Cochlear implantation (CI) has progressed considerably in recent years as highly advanced devices and surgery techniques offer a wide range of possibilities for the treatment of deafness. As a result, the criterion for cochlear implantation (CI) has shifted from a pure tone average (PTA) greater than 90 dB HL to a PTA greater than 70 dB HL and a selective loss on mid-to-high frequencies (1); even cases of mild to moderate loss (30–55 dBHL) associated with auditory neuropathy are considered for CI (2). In these cases, the

inner ear presents residual hearing; thus, it is very important to further develop CI techniques and materials that will minimally impact the cochlear mechanical integrity. The preservation of residual hearing is particularly important in cases of young children subjected to CI, and various novelties have been proposed in terms of stimulation modalities (3) or even electrode implementations using cochlear cells regeneration promoters (4,5).

The mechanical trauma caused by the insertion of a CI electrode into the inner ear has been described with animal models (6–9). A number of studies on guinea pigs by Eastwood et al. (10), Chang et al. (11), and James et al. (12) have proved that after the placement of a dummy electrode in the basal turn of the scala tympani, the high-frequency hearing (24–32 kHz) is compromised, with an immediate threshold shift of 40 dB. Ni et al. (13) found that the placement of a shorter electrode in the inner ear of

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Pietro Giordano, Silvano Prosser, Edi Simoni, Chiara Faccioli, Laura Astolfi, and Alessandro Martini received grants and support for travel from MED-EL and a grant from Cochlear Ltd. Nadia Giarbini served as a consultant for and received support for travel from MED-EL.
Supplemental digital content is available in the text.

young normal hearing kittens did not induce tissue damage distally to the electrode. This was also confirmed by Xu et al. (14) by showing that the auditory brainstem response (ABR) thresholds, in most of the cochleae tested, maintained their initial values. Both studies suggest that hair cells, at least apically to the implanted electrode, not only survive the electrode insertion but also can maintain an almost normal sensory function. Balkany et al. (15) demonstrated that preservation of otoacoustic emissions and ABR is possible after cochlear endoscopy in guinea pigs, whereas James et al. (16) evidenced that the loss of residual hearing could take place even several months after surgery, without offering a clear explanation for this delayed hearing deficit.

Among the factors, which contribute to inner ear damage after an electrode insertion, cochleosotomy is probably the most significant. The traumatic effects of cochleosotomy include the acoustic trauma caused by drilling, the alteration of cochlear homeostasis after the opening of the membranous labyrinth, and the postoperative fibrosis (17). In addition, a direct injury to the spiral ligament, basilar membrane, and osseous spiral lamina can take place at the time of electrode insertion, and the injury can be expressed either as a pure mechanical effect or as an inflammatory-immunologic foreign-body reaction. An electrode, when inserted with an inappropriate angle, can penetrate the basilar membrane, occupying the scala media or scala vestibuli. The electrodes may also directly contact the underside of the basilar membrane and/or fracture the osseous spiral lamina (18). In either case, the spiral vessel and the associated arterioles, located on the lower surface of the basilar membrane and osseous lamina, may be damaged, contributing to the loss of residual hearing. Blood and bone-dust (from drilling) may also penetrate into the inner ear, and they can propagate further, by the electrode insertion, into the scala tympani causing a significant shift of the hearing threshold (19).

The aim of this study was to use a nontraumatic implantation protocol (soft-surgery) to evaluate, in a guinea pig animal model, the hypothesis that a dummy electrode insertion can be as damage-less to the cochlea as a simple cochleosotomy. Two types of implanting electrodes were used in terms of stiffness (a soft and a stiff one). Hearing thresholds were assessed by means of compound action potentials. Hearing threshold comparisons were based on data referred to animals that had been treated with a simple cochleosotomy. The data were collected in a time window of 30 days.

MATERIALS AND METHODS

Animals

Tricolor guinea pigs, obtained from Charles River (Germany), were divided into 3 groups as follows: group A animals (31 ears) were implanted with specially designed electrodes without any contacts or wires (soft electrode, MED-EL); group B animals (22 ears) were implanted with an electrode having a metallic wire inside (stiff electrode, MED-EL); and group C animals (8 ears) underwent a simple cochleosotomy and were not implanted.

The experimental trials were approved, according to Italian guidelines given by DL 116/92, with reference to European Economic Community Directive 86–609. The animals were treated according to actual veterinary standards and were all housed under the same living conditions.

Compound Action Potential Measurements

Compound action potentials (CAP) were used to assess the auditory threshold of the animals in all 3 groups. All electrophysiologic recordings were performed in a sound-proof chamber, with the animals positioned on a homeothermic blanket. Each guinea pig was anesthetized by an intraperitoneal (i.p.) injection of 1 ml/kg (xylazine 50 mg/ml + zolazepam 50 mg/ml) + (xylazine 2% solution) before each electrophysiologic recording.

CAPs were recorded using a gold electrode permanently fixed at the bony ridge of the round window of the animal and thus allowing recording even after surgery. The CAP thresholds were recorded before cochleosotomy (baseline data); after the cochlear electrode insertion ($t = 0$ day, and at $t = 3, 7, 14$, and 30 days after surgery, CAP audiograms were obtained by stimulating the animals with clicks and Gaussian-shaped tone pips within a frequency range of 0.5 to 32 kHz (2 points/octave) and at intensities between 100 and 10 dB (in -2-dB steps, 30 averages per step). During this procedure, the contralateral ear was blocked with a foam insert to eliminate issues of cross talk.

Surgical Procedure (Soft Surgery)

Each animal was positioned on the heated operating table under strict aseptic conditions.

Before surgery, several operations were performed: (i) an i.p. injection of 0.5 ml atropine sulfate (0.5 mg/ml); (ii) a subcutaneous (sc) injection of 10 mg/kg enrofloxacin 5% solution; and (iii) ample shaving of the skin behind the pinnae, around the neck, and on the vertex of the skull. The surgical site was disinfected with povidone-iodine. Before skin incision, a local subcutaneous injection of Lidocaine-hydrochloride was administered. To place the gold wire for the CAP recording, the tympanic bulla was initially exposed by a retroauricular surgical approach so that the cochlea and the round window were visualized.

A “soft-surgery” implantation protocol was defined and adopted as follows: (a) A 1-mm cochleosotomy hole was made in the anterior-inferior region of the round window; the cochleosotomy was performed using a 0.7-mm diameter microdrill at slow speed; during the drilling a little leakage of perilymph was allowed to prevent the penetration of bone dust inside the cochlea. (b) A 3-mm insertion depth of the electrode was ensured by a dark square marker on the silicon tube that was left outside the cochleosotomy hole as a landmark for the correct positioning (Fig. 1). The angle of incidence between the electrode and the cochleosotomy was carefully monitored: the electrode had to penetrate the cochleosotomy with a dorsal to ventral direction and not perpendicularly, to allow easier insertion, without the risk of damaging the molecular wall. (c) After the electrode insertion, a small piece of muscle was placed around the electrode to seal the cochleosotomy (Fig. 2). Two drops of enrofloxacin 5% were injected into the bulla to prevent middle ear infection, and then, the bulla was closed with dental cement. Daily subcutaneous injections of enrofloxacin 5% (10 mg/kg) were administered during the 3 days after surgery and an intramuscular injection of carprofen (4 mg/kg) was given for pain relief.

Statistical Analyses

A repeated measures model was fitted using generalized estimating equations (GEE) via SAS PROC GENMOD. The response was estimated as threshold change from baseline

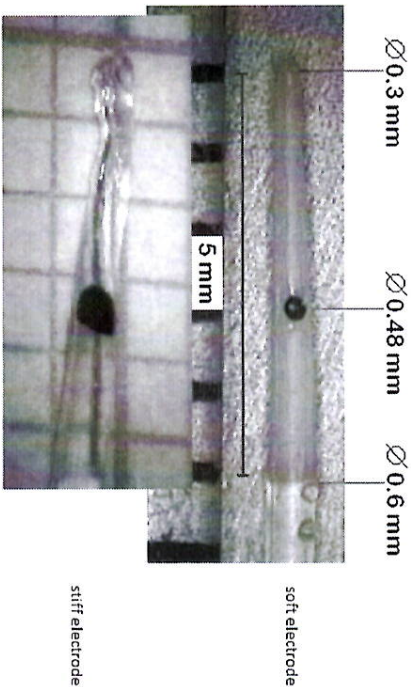


FIG. 1. The electrodes used in the study are produced by MED-EL. In both images, the black dot indicates the maximum insertion point. Both soft and stiff electrodes are of similar lengths.

(threshold at day X minus the baseline), the within factor was animal and the between factor was treatment. Individual and paired difference least squares means were obtained for each time (day), frequency, and treatment combination, and paired least squares means were obtained for each pairwise treatment difference at each time and frequency combination. The *p* values were adjusted using a stepdown-Bonferroni method with 2 levels of significance (significant at 0.05 level, and very significant at 0.01 level).

Detailed tables with the analytical data are presented as Supplemental Digital Content 1, <http://links.lww.com/MAO/A214> and Supplemental Digital Content 2, <http://links.lww.com/MAO/A215>.

RESULTS

The reference CAP threshold (baseline value) for guinea pigs was estimated by recording CAPs before conducting any surgical procedure. Data were collected from 156 ears, belonging to animals chosen for this experiment and animals, submitted to other experiments, for which the stabulatory conditions were the same. Figure 3A shows the minimum threshold at which a CAP was visible, evoked by 4, 8, 16, and 32 kHz tone-pips.

The implanted electrode was inserted approximately 3 mm along the basal turn of the cochlear duct, which, tonotopically corresponds to frequencies from 54 to 16 kHz (20), considering that the hearing spectrum of the guinea pig ear ranges from 86 to 46.5 kHz (21).

To minimize the complexity of the data, the effects of electrode insertion were evaluated within two separate bands of frequencies, termed low (4 + 8 kHz) and high (16 + 32 kHz). The average band data are displayed in Figure 3B.

High-Frequency Band

Immediately after surgery, all animals presented a hearing threshold shift with average values of 33.19 ± 4.57 dB (group A animals, soft electrode), 40.84 ± 2.88 dB (group B animals, stiff electrode) and 14.43 ± 5.02 dB (group C animals, with only cochleostomy). For the

animals of groups A and B, the shifts were highly significant (0.01 level).

At *t* = 3 d, the animals from groups A and C showed a partial recovery of the auditory threshold. No significant changes were observed in the animals of group B. The animals from group A showed the largest threshold shifts. Significant differences from the baseline values were found for group A (0.05 level) and B (0.01 level).

At *t* = 7 d, a deterioration of hearing threshold was observed in the animals of groups A and B. No significant changes were observed in the animals of group C. The animals from group B showed the largest threshold shifts. Significant differences (0.01 level) from the baseline values were found in both groups A and B.

At *t* = 14 d, the responses from groups A and B were improved (in comparison to the data of *t* = 7 d). No

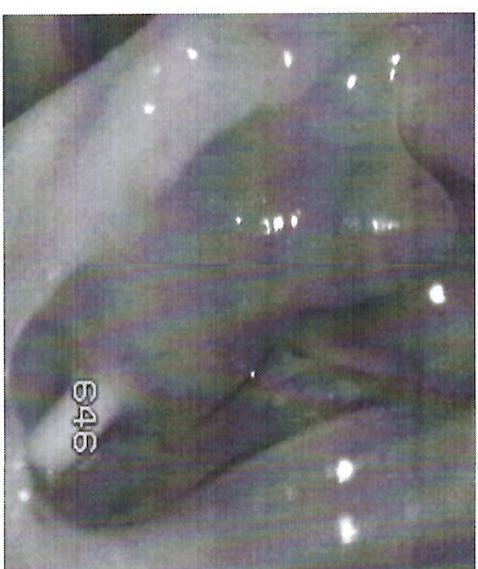


FIG. 2. The cochlea of a guinea pig after explantation. The electrode (No. 646) seems to be appropriately inserted (i.e., the CI black dot marker is not visible).

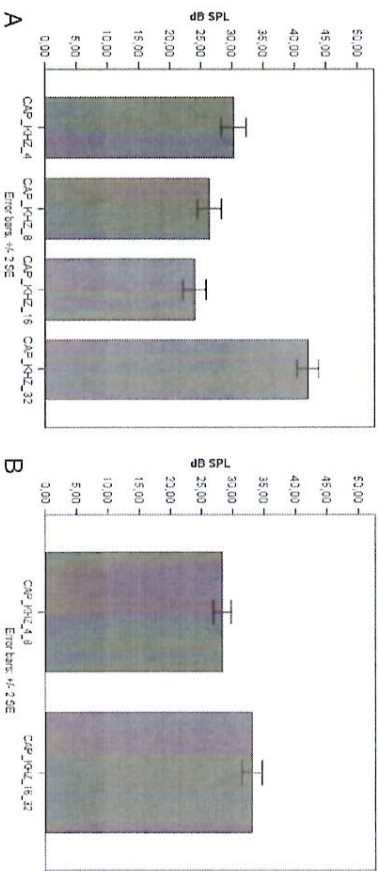


FIG. 3. Average CAP thresholds (in dB SPL) from 156 untreated ears, evoked by 4, 8, 16, and 32 kHz tone pips. Left panel (A): averages at each tested frequency. Right panel (B): Averages from the low- and high-frequency band, which were used in the estimation of the baseline responses.

significant changes were observed in the animals of group C. The animals from group B showed the largest threshold shifts. Significant differences from the baseline values were found for group A (0.05 level) and B (0.01 level).

At $t = 30$ d, the responses from groups B and C showed an additional recovery, whereas those from group A showed an additional deterioration. No significant changes were observed in the animals of group C. The animals from group B showed the largest threshold shifts. Significant differences (0.01 level) from the baseline values were found for both groups A and B.

Overall, the threshold patterns across the 3 groups show an oscillatory behavior. Analytically, there is a threshold recovery at Day 3 (very marked for group A). At Day 7, there is a global deterioration of the hearing threshold (mainly in groups A and B). At Day 14, there is another global threshold recovery. At Day 30, the hearing threshold in groups B and C improves, while it further deteriorates in Group A. The high-frequency data are summarized in Figure 4.

Low-Frequency Band

Immediately after surgery, all animals presented a hearing threshold shift with average values of 14.09 ± 3.39 dB (group A animals, soft electrode) and 9.01 ± 3.37 dB (group B animals, stiff electrode) and 9.01 \pm 3.37 dB (group C animals, only cochleostomy). For the animals in groups A and B, the shifts were highly significant (0.01 level).

At $t = 3$ days, the animals from groups A and C showed a partial recovery of the auditory threshold. The animals from group B showed the largest threshold shifts. Significant differences from the baseline values were found for group A (0.05 level) and B (0.01 level).

At $t = 7$ days, the animals from groups B and C showed an additional recovery of the auditory threshold. The animals of group A presented an additional threshold deterioration. The animals from group B showed the largest threshold shifts. The threshold shifts in groups A and B were highly significant (0.01 level).

At $t = 14$ days, all animals showed an additional threshold recovery. The animals from group B showed the

largest threshold shifts. Significant differences (0.01 level) were only observed in this group.

At $t = 30$ days, the responses from groups A and B showed a marked threshold deterioration. The animals from group B showed the largest threshold shifts. The threshold shifts in groups A and B were highly significant (0.01 level).

Overall, the threshold patterns for the low frequency band, across the 3 groups, show a different trend compared with the high-frequency band. The threshold shifts were smaller by a margin of approximately 20 dB (mainly groups A and B). Group C showed a linear recovery pattern, without the oscillations observed in the high-frequency band. Groups A and B showed a threshold recovery till Day 14 and thereafter a delayed threshold deterioration. The low-frequency data are summarized in Figure 5.

Differences Across the 3 Groups

The main pattern that emerged from the data comparison (the detailed statistical values are presented

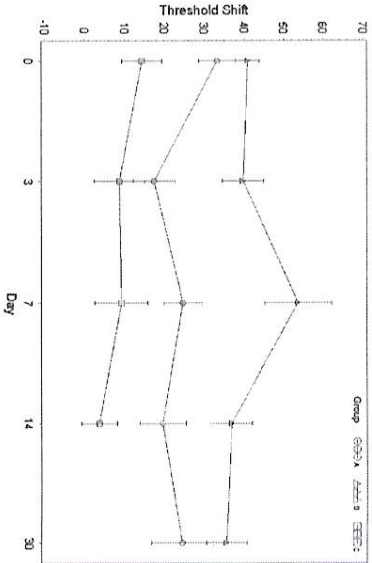


FIG. 4. Average threshold shifts (\pm SE) in dB SPL at the high-frequency band (16 + 32 kHz). Average responses are shown immediately after surgery ($t = 0$ d) and at $t = 3, 7, 14$, and 30 days postoperatively. The standard error estimates are reported in Supplemental Digital Content 1, <http://links.lww.com/MAO/A214>. Significant threshold shifts (in comparison to baseline values) are reported in the text.

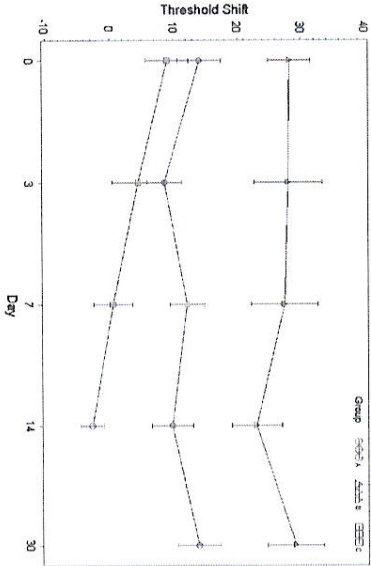


FIG. 5. Average threshold shifts (±SE) in dB at the high frequencies (4 + 8 KHz). Average responses are shown immediately after surgery (*t* = 0 d) and at *t* = 3, 7, 14, and 30 days postoperatively. The standard error estimates are reported in Supplemental Digital Content 1, <http://links.lww.com/MAO/A214>. The presence of significant threshold shifts (in comparison to baseline values) is reported in the text.

in the Table. Supplemental Digital Content 2, <http://links.lww.com/MAO/A215>) is that the 2 electrode approaches result in nonstatistically significant threshold shifts. This observation is valid for both frequency bands.

From a comparison of groups A and C, the following trends were identified: (i) for the high frequencies, no significant differences were found; (ii) for the low frequencies, significant differences (*p* = 0.0208) emerged only at *t* = 14 days.

From a comparison of groups B and C emerged that at all observation times, and both at low and high frequencies, the responses from group B were statistically different (at a 0.01 level) from the responses from group C. Only at time *t* = 3 days the difference was significant at a 0.05 level.

To summarize the differences: The responses from group A are positioned between the responses of group C (lower shifts) and group B (higher shifts) and this explains the lack of significant differences between A-C (except at *t* = 14 d) and A-B. The difference between B-C, as measured by the standard error, is large and therefore statistically significant.

DISCUSSION AND CONCLUSION

The objective of the article was to assess the effects of electrode insertion on the hearing function of guinea pigs and compare them with the effects of a simple cochleostomy.

The data show that cochleostomy causes a slight increase in hearing threshold, from 9.01 dB SPL to 14.43 dB SPL in the low- and high-frequency bands, respectively, but a recovery process is visible already from Day 3. During the 14-day observation window, the hearing threshold recovers almost completely.

The insertion of cochlear electrodes produced a consistent deterioration of the hearing threshold in compari-

son to baseline values, immediately postsurgery and during the 30-day observation window. The insertion of the rigid electrode (group B animals) produced a greater increase in threshold than the soft electrode (group A animals). This was observed in both low- and high-frequency bands, although the differences of the threshold shifts were not found statistically significant. In this context, 2 scenarios can be considered: (i) it is plausible that the insertion of the rigid electrode is associated with a major mechanical trauma of the cochlear partition; and (ii) the presence of a rigid electrode alters the cochlear hydrodynamics more effectively, in comparison to the effects of a soft electrode.

Disregarding the immediate threshold deterioration at *t* = 0 d, probably caused by surgical trauma, the threshold at low frequencies (Fig. 5) shows a progressive and delayed deterioration, starting from the 14th day of observation. The observed threshold shifts were evidently produced within a cochlear region that was not in contact with the electrode, and the effects could be interpreted as the result of an apical diffusion of inflammation. The effects of an endocochlear fibrosis in the vicinity of an electrode have been demonstrated by assessing the correlations between hearing and histology (22). Choi and Oghehlat (17) used a 1-dimensional mathematical model to predict the attenuation of basilar membrane vibrations because of a fibrotic process localized in the scala tympani. This condition leads to a substantial delay in the propagation of vibrations along the basilar membrane, with a consequent increase in the local impedance.

The results obtained in this study could be explained by the following mechanism: the threshold in the high frequencies remains steadily raised over time, reflecting a disturbance of cochlear mechanics, caused by the presence of the electrode. The volume of an electrode (soft/rigid) inserted 3 mm into the cochlea occupies at least 4/5 of the scala tympany. This probably reduces the differences in pressure, normally applied to scala vestibuli through the oval window, resulting in an alteration of the local hydrodynamics. The process of fibrosis could be considered responsible for a deterioration of hearing threshold (after Day 14) in the low frequencies. The process, which develops around the electrode, is similar to a foreign body reaction (17) and has been well documented. It could be hypothesized that the apical region of the cochlea continues to experience a poor spread of mechanical energy coming from the basal region. This poor transduction, because of a progressive fibrous filling of the scala tympani, could further reduce the transmission speed of vibration, increasing the attenuation of the basilar membrane oscillation at low frequencies.

The low-frequency data emerging from this study, which offer an explanation of the induced hearing loss at apical frequencies distant from the electrode position, are in apparent contrast with the data reported by Kieffer et al. (23). According to their results, the presence of an electrode in the scala tympani may affect the mechanics of the cochlear region adjacent to the electrode but will not influence regions distant from the electrode, that is, apical

frequencies. This hypothesis is supported by histologic observation on human cadavers, but it might not be applicable to the guinea pig model, given the large volumetric differences in the respective tympanic scalae (24). In the guinea pig, the volume of the first 3 to 4 mm of the basal scala tympany (with a cross-section area ranging between 0.6 and 1.2 mm) is almost completely occupied by the electrode. In this context, the presence of the electrode impedes the normal transfer of mechanical energy to the apical regions of the basilar membrane.

The data reported in this study show that a soft-surgery approach and a soft electrode can reduce the mechanically induced threshold shifts. The data suggest that, although it is possible to reduce the mechanical damage to the cochlea, it is not possible to completely eliminate the induced threshold shifts, after the insertion of a cochlear electrode. A comparison of histopathology between the 2 treatment groups will be the topic of a different article.

It might be possible to limit and reduce the damage created by long-term fibrotic processes and/or by the postoperative phenomena of scarring. A possible approach might be the use of electrodes that release locally otoprotective drugs. This alternative solution has been examined as well and will be developed in a specific manuscript.

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