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Predictors of Fibrotic and Bone Tissue Formation with 3-D Reconstructions of Post-Implantation Human Temporal Bones

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Abstract

Hypothesis: Years of implantation, surgical insertion approach, and electrode length will impact the volume of new tissue formation secondary to cochlear implantation.

Background: New tissue formation, fibrosis and osteoneogenesis after cochlear implantation have been implicated in increasing impedance and affecting performance of the cochlear implant.

Methods: 3-D reconstructions of 15 archival human temporal bones from patients with a history of cochlear implantation (CI) were generated from H&E histopathologic slides to study factors which affect volume of tissue formation.

Results: Years of implantation was a predictor of osteoneogenesis (r=0.638, p-value=0.011) and total new tissue formation (r=0.588, p-value=0.021), however not of fibrosis (r=0.235, p-value=0.399). Median total tissue formation differed between cochleostomy and round window insertions, 25.98% and 10.34%, respectively (Mann-Whitney U=7, p=0.018). No correlations were found between electrode length or angular insertion depth and total new tissue (p=0.192, p=0.35), osteoneogenesis (p=0.193, p=0.27), and fibrosis (p=0.498, p=0.83), respectively. However, the type II error for electrode length and angular insertion depth ranged from 0.73 to 0.90, largely due to small numbers of the shorter electrodes.

Conclusions: With numbers of cochlear implant recipients increasing worldwide, an understanding of how to minimize intracochlear changes from implantation is important. The present study demonstrates that increasing years of implantation and inserting electrodes via a cochleostomy compared to a round window approach are associated with significantly greater degree of new tissue volume formation. While prior studies have demonstrated increased intracochlear damage in the setting of translocation with longer electrodes, length and angular insertion depth of CI electrodes were not associated with increased tissue formation.

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Competing Interests

The authors have no conflicts of interest to disclose.

Introduction

Cochlear implantation is a valuable tool providing hearing to patients with severe to profound hearing loss. One of the challenges with cochlear implantation is minimizing the secondary intracochlear changes following electrode placement in the inner ear. Intracochlear changes can occur via direct primary mechanical damage to structures or through secondary inflammatory cascades following implantation, such as fibrosis and osteoneogenesis[1–3]. Cochleostomy with resultant cochlear endosteum damage has been implicated as a trigger of new tissue formation and has been shown to be associated with endolymphatic hydrops[4]. Translocation of longer electrodes has been demonstrated to be associated with a higher degree of intracochlear damage with lateral wall injury and poorer auditory outcomes[5].

Damage to the cochlear endosteum can trigger fibrosis and osteoneogenesis causing blockage of the ductus reuniens leading to secondary endolymphatic hydrops and subsequent residual hearing loss[4]. When the endolymphatic hydrops extends to the utricle and semicircular canals, patients can suffer from vertigo and imbalance[6]. New tissue formation increases impedance from the CI electrodes to the spiral ganglion neurons, causing higher levels of energy consumption of the electrode[2,7–10]. In animal and humans models, new tissue formation has been reported to negatively impact spiral ganglion neuronal (SGN) survival[2,11]. One proposed mechanism of SGN death is damage to surrounding structures including hair cells and schwann cells which support the survival of SGNs through release of neurotrophins and neuroregulin[12,13]. Clinically, postoperative consonant-nucleus-consonant (CNC) scores have been shown to negatively correlate with the percent volume of new bone[14] and to negatively impact residual hearing[15]. New tissue formation can also affect subsequent surgeries, making explantation or reimplantation more difficult[16].

Fayad and Linthicum reported that the years of implantation and age of the patient at implantation did not affect the amount of new tissue formation[17]. Studies by Somdas and Li noted that damage to the lateral wall correlates with new tissue formation and additionally a trend for increased new bone formation with a longer duration of implantation[18,19]. Identifying factors to minimize CI-induced intracochlear tissue formation is important to maintain the long-term cochlear health especially since increasing number of patients with residual hearing and infants of young age are undergoing cochlear implantation. The aim of the present study is to elucidate the predictors of tissue formation in cochlear implantation, including duration of implantation, approach used to place the electrode in the cochlea (round window vs cochleostomy), and electrode degree of insertion and length.

Methods

Temporal bone harvesting

Included in this study are 15 human temporal bones (HTBs) from patients who had received a cochlear implant for ototoxicity, meningitis, otosclerosis, or hereditary hearing loss. Table 1 details the descriptive information of this study's temporal bones. The Institutional Review Board (IRB) of UCLA approved this study (IRB protocol #10–001449). All methods used in

this study are in accordance with NIH and IRB guidelines and regulations. Appropriate informed consent had been obtained from each patient before inclusion in the study. The temporal bone donors were part of the National Institute of Health funded National Temporal Bone Laboratory at UCLA through the National Institute on Deafness and Other Communication Disorders. The medical history for each of the patients who had donated their temporal bones is maintained and preserved in a secured electronic database.

HTB processing: The temporal bones had been removed postmortem and placed in 10% neutral buffered formalin for three weeks, decalcified in EDTA until shown by X-ray to be free of calcium. Embedding was done in increasingly concentrated celloidin to allow complete penetration. To minimize extraction movement and the effect of chloroform-induced swelling of the silicone, the electrode was removed just before the specimen was placed in hardening chloroform. The celloidin block was then cut into 20-micron sections of which every tenth was mounted and stained with hematoxylin and eosin (H & E). The stained human temporal bone sections were examined using a light microscope (Nikon Alphaphot YS) and all images were captured using a digital camera (Optromics).

3-D Reconstruction of the Cochlea using Amira 6.5

A total of 15 human temporal bones were used in this study. There were 8 male and 7 female subjects; and there were 7 right and 8 left temporal bones. The digital images captured of serial H&E sections were reconstructed into 3-D models. Images (between 28–39 sections per specimen) were taken of the entire cochlea using a light microscopy objective (1x), total magnification 10x. The images were aligned using identifying landmarks (fiduciary points), including the cochlea, internal auditory canal, saccule, and semicircular canals, with the Fiji (Fiji Is Just ImageJ) software program, using the TrakEM2 plugin. Hyperstacks of the aligned images were then created on Fiji to account for the nine unstained sections between every H&E section. The hyperstack was then loaded onto Amira (version 6.5.0) where 3-D reconstructions were generated. Using the ‘Segmentation’ tool of Amira, the entire cochlea was manually segmented on every H & E slide in the hyperstack. Once the cochlea was segmented on all the H & E slides, the volume between segmented sections was interpolated to create a complete 3-D rendering of the cochlea. Similar manual segmenting and automatic interpolation were utilized to create 3-D renderings of the fibrotic and osseus tissue. To input the dimensions of each voxel on Amira, 1x images taken with the light microscope were measured to determine microns per pixel. Using Amira allowed for the examination of the 3-D models from different angles and if needed, the manual adjustment of automatic interpolations. Additionally, the 3D renderings on Amira allowed us to accurately measure the degree of insertion of the electrode from the round window (the protocol and coordinate system for degree of insertion measurements are discussed in the following sections).

Measuring new tissue formation

Tissue formation inside the cochlea was measured on Amira. New tissue formation post-implantation is either fibrotic or bone in nature. Similar to the process of generating the cochlea described above, 3-D reconstructions were made of the fibrosis and new bone formation inside the cochlea. Then using the ‘Measure and Analyze’ tool in Amira, the respective volumes of these tissue types were calculated. Proportions of tissue formation

were defined as total tissue (i.e., fibrosis, bone, or combined) divided by cochlear volume (i.e., scala tympani, scala vestibuli, and scala media). Exclusion criteria was presence of osteogenesis in the corresponding non-implanted temporal bone and/or radiographic or operative report with mention of ossification at round window or inside scala tympani.

Degree of insertion

Degree of insertion of the electrode from the round window was measured using the coordinate system established by Verbist et al. (2010)[20]. Since the histology sections used in this study were sectioned after removal of the electrode, the indication of insertion depth was surrounding tissue formation or damage to surrounding structures. The angular measures were then made using Amira's 2-D angle tool while positioning the 3-D reconstruction in the 'cochlear view', defined as viewing the cochlea through the z-axis from the helicotrema to the base of the cochlea.

Not every temporal bone exhibited histologic changes that allow for the determination of the final termination point of the electrode. Therefore, the degree of insertion of CI electrodes was able to be measured for 12 of the 15 temporal bones.

Statistics

Statistical analysis was conducted using SPSS. Pearson correlation coefficients were computed to assess the relationship between variables. Mann-U-Whitney test was conducted to compare cochleostomy and round window insertion groups. ANCOVA was used for multivariate analysis; categorical variables were inputted as 'fixed factors' and continuous variables as 'covariates'. The significance threshold was set at $p<0.05$. G Power (version 3.1.9.7) was used to calculated type II errors (β).

The approach for statistical analysis was to examine relationships using univariate analysis followed by multivariate analysis. A Pearson correlation or Mann-U-Whitney was used to identify single variable correlations. Significant predictors from Pearson correlation and Mann-U-Whitney analysis were run in ANCOVA analysis to determine the effect in a multivariate model.

Results

Years of implantation affects total tissue, bone formation, and bone/new tissue

Pearson correlation was used to investigate the relationship between total years of implantation and tissue formation outcomes. Years of implantation was a predictor of bone formation (Figure 2B; r=0.638, p-value=0.01, β=0.22) and total new tissue formation (Figure 2A; r=0.588, p-value=0.02, β=0.32), however was not a predictor of fibrosis (r=0.235, p-value=0.39, β=0.86). It did however correlate with new bone/new tissue (r=0.515, p-value=0.04) indicating that as years progress, bone tissue comprises a larger proportion of the total tissue. TB 11 (Figure 1) with 24 years of implantation had the most extensive tissue formation, where the entire cochlea up to 360 degrees was filled by either fibrosis or osteoneogenesis.

Cochleostomies cause more total tissue and fibrosis than round window approaches

There was significantly greater amount of median total tissue formation in the cases of CI insertion by cochleostomy (25.98%) compared with cases of CI insertion by the round window approach (10.34%) (Mann-Whitney U=7, p=0.018 two-tailed). Since years of implantation was also a predictor of total new tissue formation, ANCOVA analysis with insertion type and years of implantation was conducted. In the ANCOVA model, insertion technique and years of implantation had significant effects on new tissue formation: F(2,12)=6.15, p=0.01, with p-values for years of implantation (p=0.07) and insertion type (p=0.07) approaching significance. Figure 3 is a scatterplot comparison between round window and cochleostomy surgical insertions as a function of years of implantation and demonstrates a trend towards more tissue formation with the cochleostomy approach and duration of implantation. Using ANCOVA to control for years of implantation, the effect of CI surgical approach on new bone formation was not observed F(2,12)=4.56, p=0.03, with p-values for years of implantation (p=0.03) and insertion type (p=0.48). The temporal bone with the least amount of tissue formation is Temporal Bone ID 2 which was implanted using a round window approach for a duration of 6 years. Evidenced in Figure 4, 2% of its cochlear volume contained tissue in the form of fibrosis with no evidence of osteoneogenesis.

Length of the electrode did not correlate with tissue formation

With regard to tissue formation related to the electrode length, two potential predictors of new tissue formation were evaluated: length of the CI electrode and the angular degree of insertion. While an electrode of a certain length implanted in different cochleas will translate to the same length of foreign material exposure, the angular degree of insertion may vary based on individual cochlear size and trajectory travelled by the electrode in the scala tympani. It is important to note that the histology slides and 3-D reconstructions reveal that new tissue formation is localized to the length of the CI electrodes and does not extend further apically. Figure 5 demonstrates that new tissue formation terminates near the apical end of the CI electrode. However, the present study does not show a correlation between the electrode length or degree of insertion of the electrode with the volume of new tissue formation. No correlation was found between electrode length and total new tissue (p=0.19, β=0.74), total bone (p=0.193, β=0.74), nor total fibrosis (p=0.49, β=0.90). In an ANCOVA model, controlling for years of implantation did not reveal an effect of electrode length on total new tissue (p=0.16) or bone formation (p=0.15). Controlling for insertion type did not change outcomes for the effect of electrode length on total new tissue (p=0.89) and total fibrosis (p=0.55).

Similarly, no correlation was found for the degree of insertion and total new tissue (p=0.35, β=0.85), total bone (p=0.27, β=0.80) and total fibrosis (p=0.83, β=0.93). In an ANCOVA model, controlling for years of implantation did not change outcomes for the effect of degree of insertion on total new tissue (p=0.41) or bone formation (p=0.26). Controlling for insertion type did not change outcomes for the effect of degree of insertion on total new tissue (p=0.98) and total fibrosis (p=0.39).

Discussion

The formation of new tissue surrounding the CI following implantation is associated with higher impedances, more poor speech performance, and loss of both dendrites and spiral ganglion neuronal counts due to changes in the biophysical properties of the cochlear microanatomy[15,17]. This study aims to investigate potential predictors of post-implantation fibrotic and bone tissue formation using 3-D reconstructions generated from H&E histopathologic slides from patients with a history of cochlear implantation. Years of implantation and surgical insertion technique by cochleostomy were associated with increased new tissue formation while electrode length and degree of electrode angular insertion depth were not statistically significant. There appears to be intersubject variability in the degree and type of new tissue formation following placement of the CI electrodes in the cochlea. It is important to note that the type II error for statistical analysis of the effect of electrode length and angular insertion was high due to small sample size of the shorter electrodes.

Duration of cochlear implant use is associated with more total new tissue and bone formation. Years of implantation positively correlated with total new tissue and bone formation, meaning that the duration of cochlear exposure to the implant is a significant factor. This is particularly important for the increasing number of implanted infants who will be lifelong cochlear implant users. This is critical given that multiple studies demonstrate earlier activation of CI electrodes (before 6 months of age) results in progressively better speech perception outcomes[21,22]. Moreover, years of implantation positively correlated with the bone to new tissue ratio, indicating that with time, bone comprises a larger volume of the total new tissue. This may indicate that fibrotic tissue is a precursor to osteoneogenesis and some of the initial fibrotic tissue transitions to bone with time.

Cochleostomy insertion is associated with more total new tissue and fibrosis. Studies have shown that the most intense inflammatory response occurs at the site of electrode insertion[23], and therefore the present study compared cochleostomy and round window insertion approaches. Prior studies have shown that the cochleostomy insertion is associated with more intracochlear trauma compared with the round window insertion approach and the mechanism of damage is multiple[4–6,24–27]. Cochleostomy disturbs the cochlear endosteum and can trigger fibrosis and osteoneogenesis causing blockage of the ductus reuniens, leading to secondary endolymphatic hydrops which may cause delayed loss of residual low frequency hearing[5,6]. In addition, the cochlear hydrops that occurs in the setting of cochleostomy may be associated with postoperative spells of vertigo and dizziness when the hydrops extends to the vestibule[6]. The findings of our study corroborate prior studies demonstrating that the cochleostomy approach causes more fibrosis and total new tissue formation compared with the round window insertions. In an ANCOVA model analyzing the effects of insertion type and years of implantation on total new tissue formation, the model was significant $F(2,12)=6.15$, $p=0.01$, with p-values for years of implantation ($p=0.07$) and insertion type ($p=0.07$). Minimizing insertion trauma is an important consideration for the surgeon and the present study findings suggest that the round window insertion is recommended to minimize new tissue formation.

While prior studies have shown that new tissue formation is generally found along the track of the electrode[18], it is interesting that the present study did not reveal a correlation between new tissue formation and electrode length or degree of insertion. Interindividual anatomic differences may account for the lack of correlation. Danielian et al. (2020) noted a high degree of interindividual variance of cochlear angular and linear duct lengths (ranging from 35.44 mm to 43.57 mm) while spiral ganglion neuronal length at the inner wall exhibited less variance (ranging from 16.34 mm to 18.92 mm). These variances in total cochlear length and volume may have an influence on the degree of new tissue formation for a given CI electrode length[28]. A study by Lo et al. (2017) on guinea pigs, found a significant effect of depth of insertion on tissue formation at 4 weeks post-implantation[29]. It is possible that during the early stages of post-implantation, insertion depth has a role in the initiation of new tissue formation, but in the later stages, factors including years of implantation and the route of electrode insertion (cochleostomy vs. round window insertion) have stronger effects on overall tissue formation, masking the effects of insertion depth or electrode length. In a prior study, Ishiyama et al. (2019) noted that in cases of translocation of the electrode, longer electrode insertions were associated with a greater degree of damage to the lateral wall.[5] Alternatively, one of the primary concerns in the present study is the large type II errors for electrode length and degree of insertion correlations, ranging from 0.73 to 0.90, due to the small number of shorter electrodes. False lack of rejection of the null hypothesis is a possibility so larger sample sizes and analysis of more confounding predictors would elucidate the effects of electrode length and angular insertion depths on tissue formation more clearly.

In addition to optimizing surgical technique using atraumatic insertion and the round window approach when possible, there is also an interest in the application of steroids to minimize new tissue formation. Steroid eluting electrodes have been reported to decrease tissue formation[8,30–32]. While the mechanism is not entirely understood, steroids are used in a variety of medical conditions for their anti-inflammatory effects, and have been shown to suppress growth of fibroblasts in vocal fold, tracheal and esophageal tissues[33]. Similar mechanisms may allow for the reduction of new tissue formation in the cochlea.

One limitation with the current study is the small sample size. A larger sample size would increase the power and sensitivity to detect smaller effects on new tissue formation. Additionally, there may be other predictors that play an important role in tissue formation that were not analyzed in the present study. For example, tissue formation may be influenced by the etiology of the hearing loss and future studies analyzing this relationship should be explored. Finally, all the temporal bones are harvested from individuals implanted in adulthood, so it would be important to analyze temporal bones from patients who had been implanted at younger ages.

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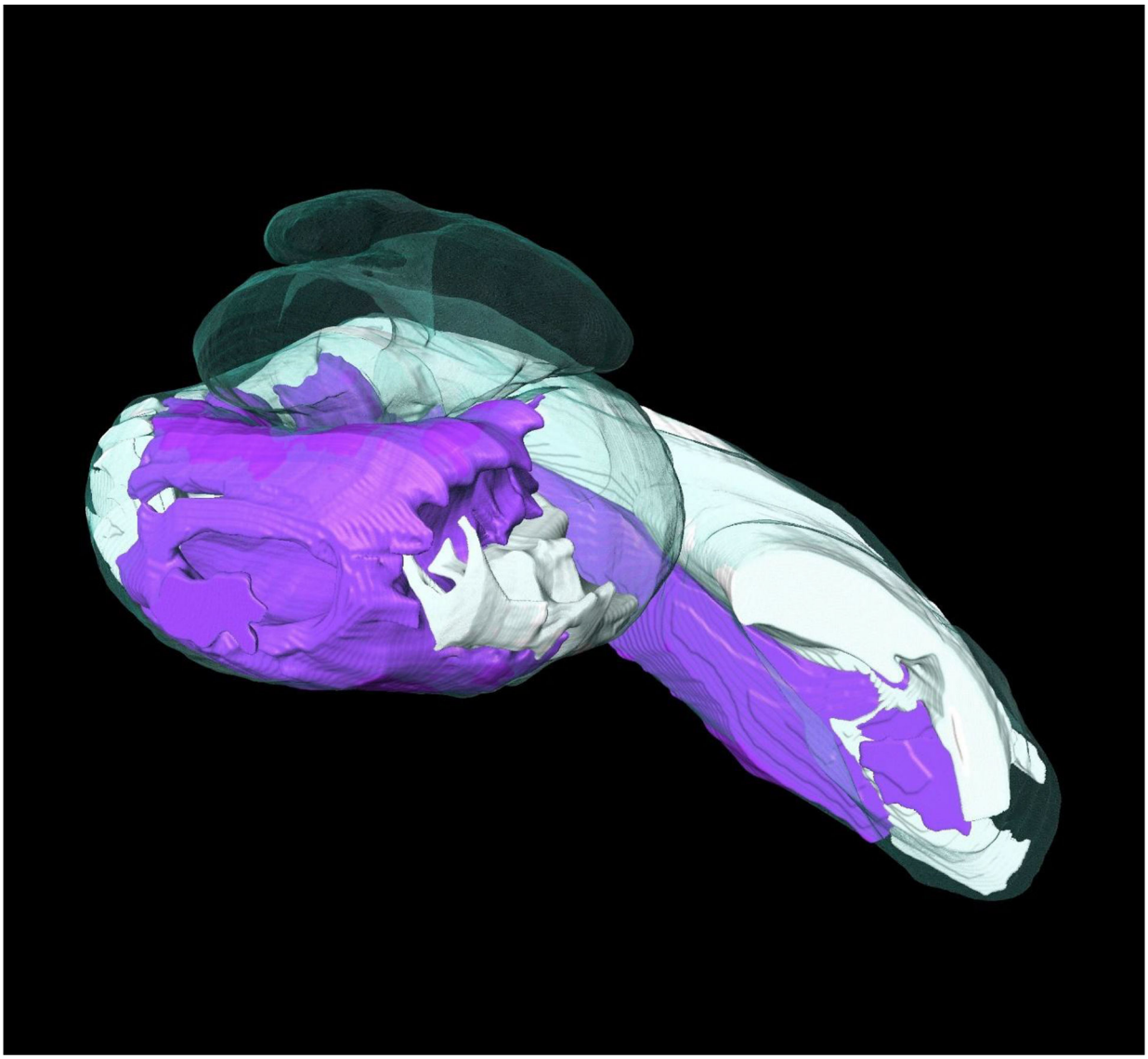

Figure 1:
3-D reconstruction of TB 11. Longest years of implantation in the sample set at 24 years and most extensive tissue formation at 50% of the cochlear volume. The entire cochlea up to 360 consists of either fibrotic (white) or bone (purple) tissue.

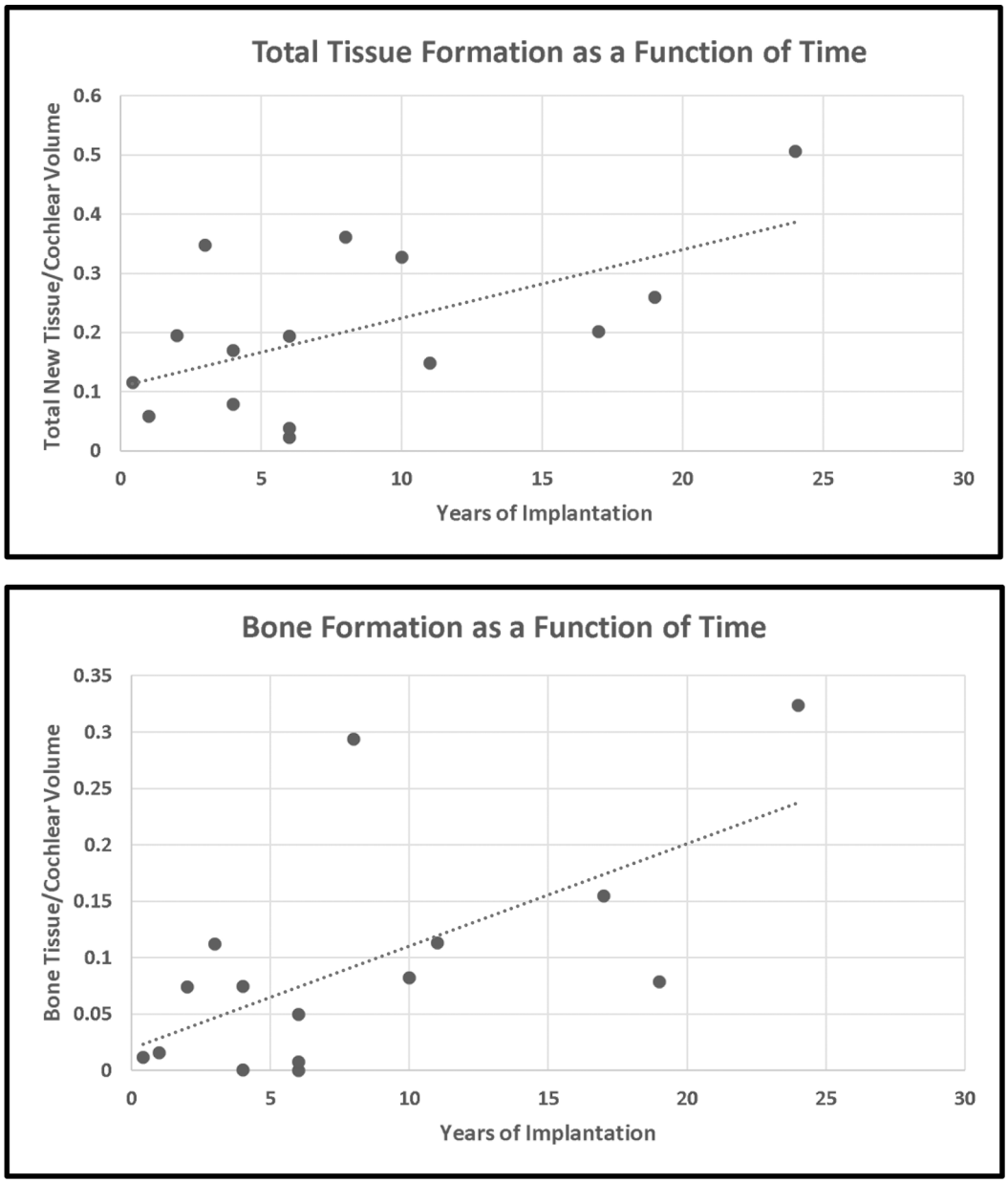

Figure 2:

Years of implantation and tissue formation. Figure 2A is a scatterplot of years of implantation and total tissue formation, with a Pearson correlation r=0.588 (p=0.02). Figure 2B is a scatterplot of years of implantation and bone formation, with a Pearson correlation of r=0.638 (p=0.01).

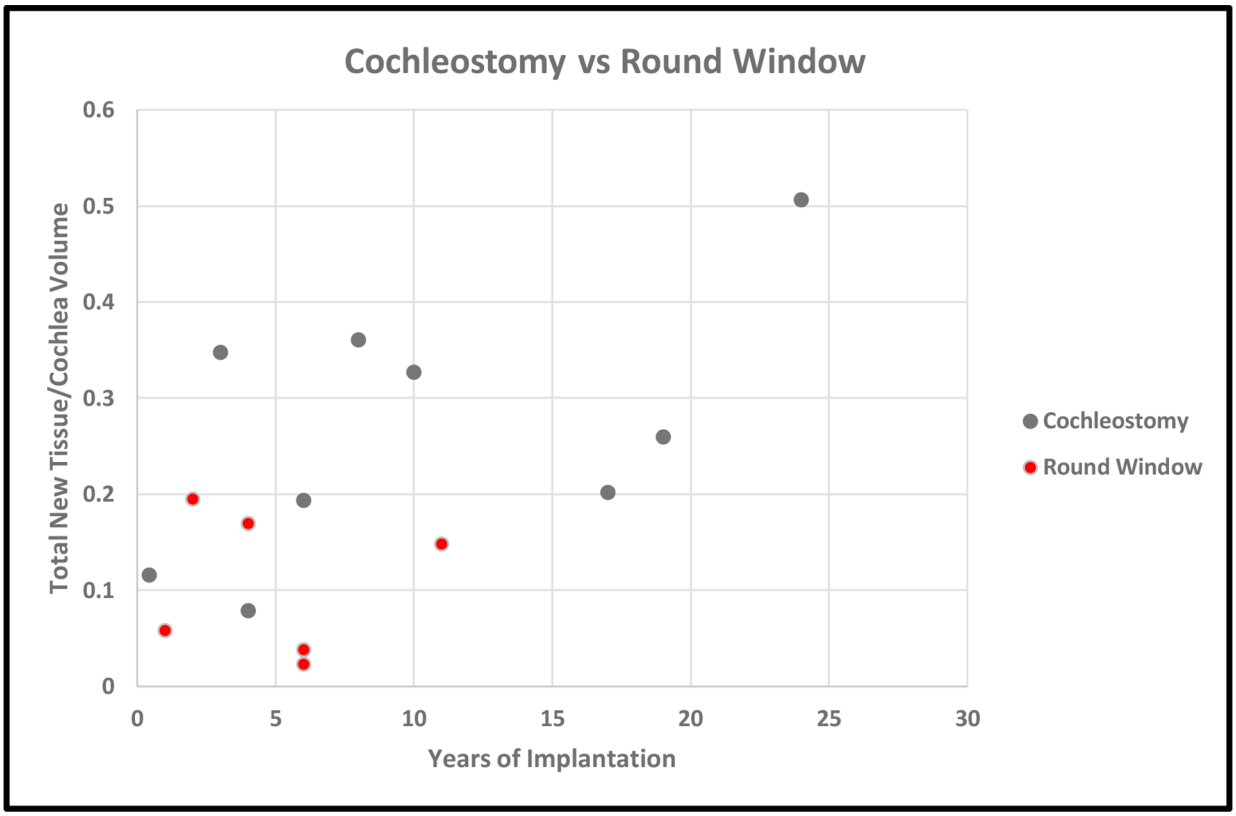

Figure 3:

Cochleostomy vs round window surgical insertion. Median total tissue formations in cochleostomy and round window insertions were 25.98% and 10.34%, respectively; the distributions in the two groups differed significantly (Mann-Whitney U=7, p=0.02 two-tailed). Since years of implantation was also a predictor of total new tissue formation, ANCOVA analysis with insertion type, years of implantation and total new tissue was performed: the model was significant (p=0.01) with p-values for years of implantation (p=0.07) and insertion type (p=0.07) approaching significance.

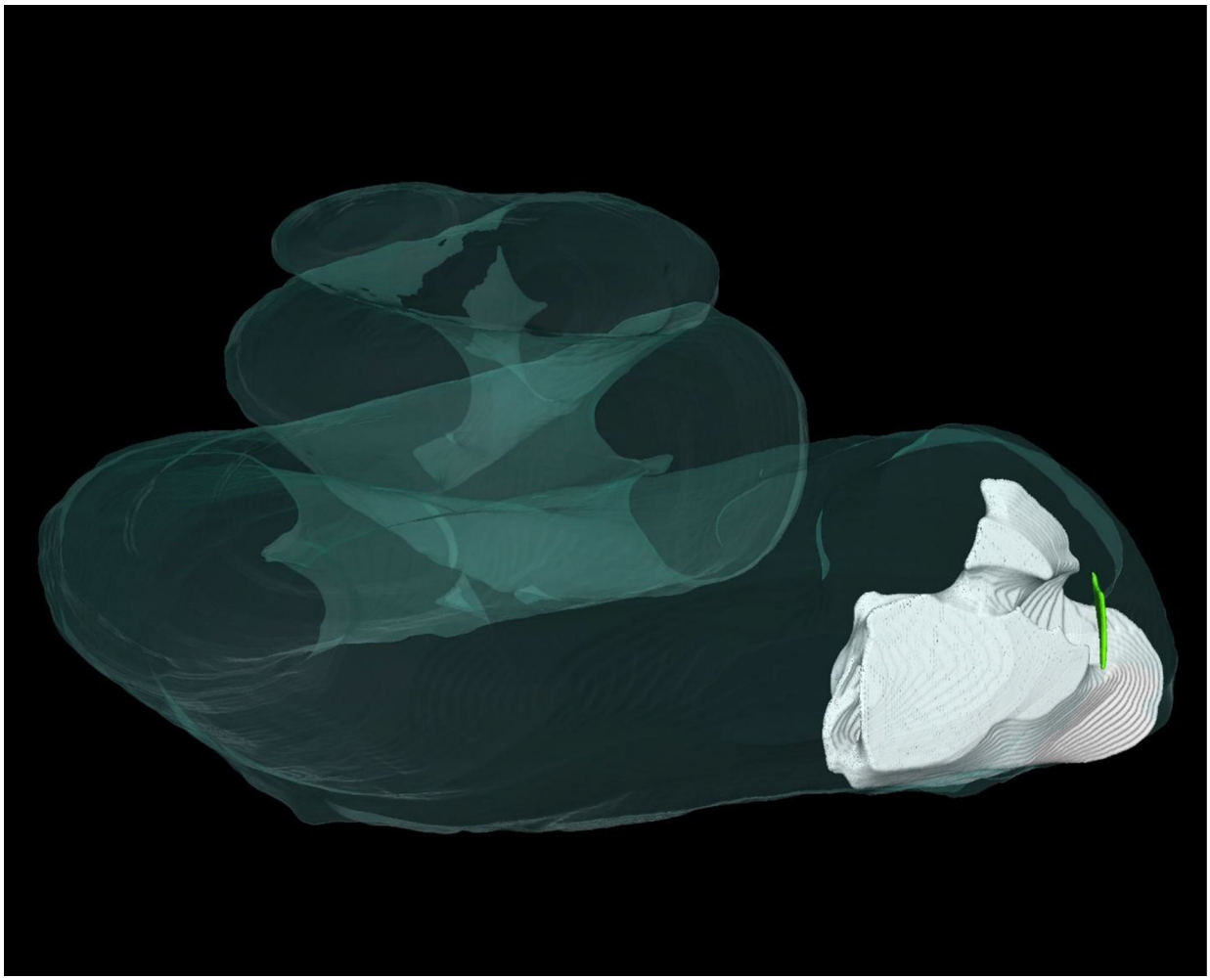

Figure 4:

3D reconstruction of Temporal Bone ID 2. Least extensive tissue formation in sample. Round window insertion of 6mm electrode that was implanted for 6 years. Minimal fibrotic tissue (white) near the round window (green) with no evidence of bone formation. White=fibrosis; green=round window

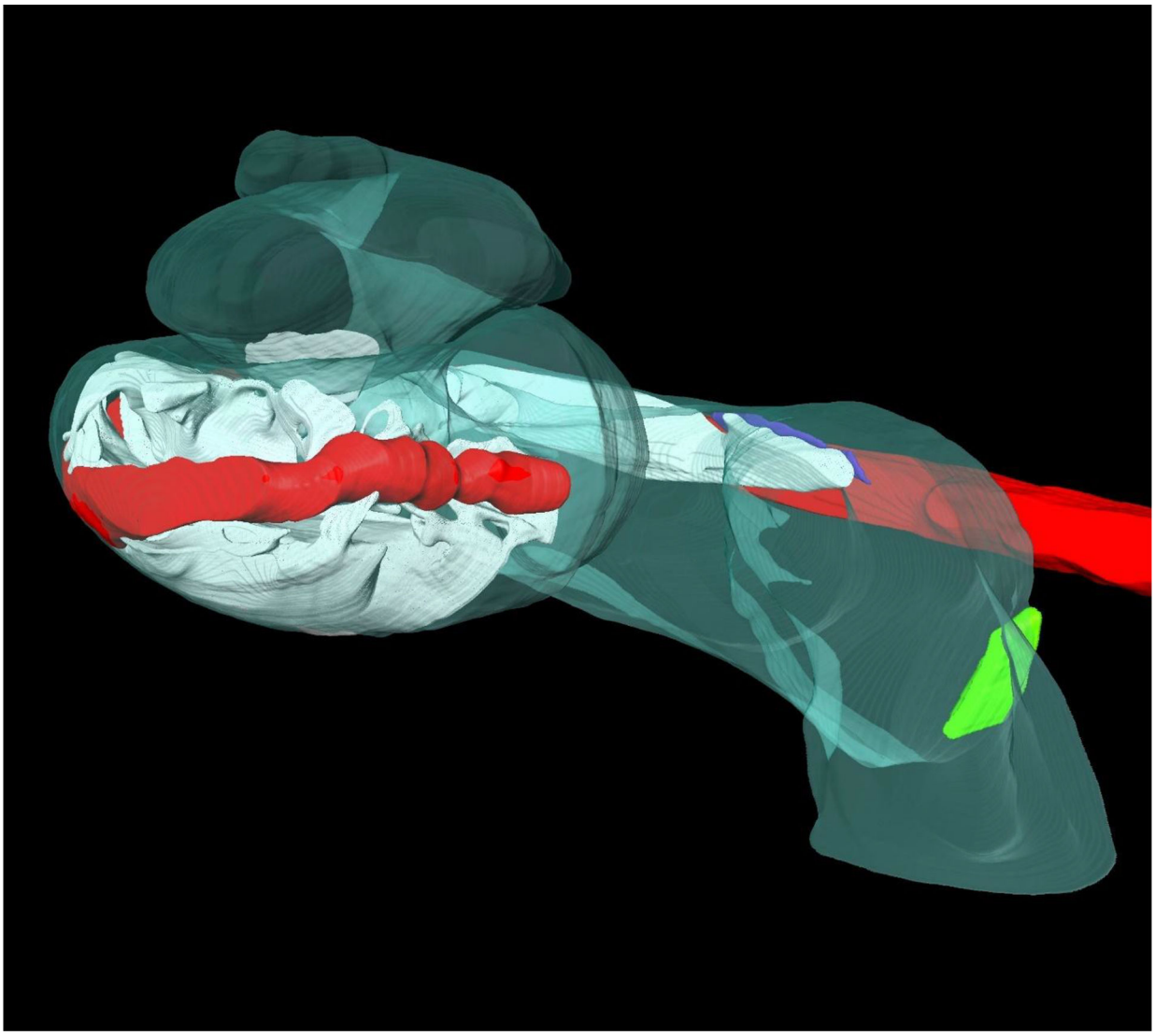

Figure 5:

3D reconstruction of Temporal Bone ID 4. Tissue formation is found adjacent to the electrode and does not extend more apically than the electrode tip. However, analysis showed that the volume of tissue formation did not correlate with electrode length and degree of insertion. No significant correlation was found between electrode length and total new tissue (p=0.19), total bone (p=0.19), and total fibrosis (p=0.49). No significant correlation was found for between degree of insertion and total new tissue (p=0.35), total bone (p=0.27), and total fibrosis (p=0.83).

Red=cochlear implant electrode; green=round window; white=fibrosis; purple=bone

Table 1:

Descriptive information of the fifteen post-implantation human temporal bones used in the study.

Temporal bone ID	Insertion type	Degree of Insertion	Electrode Length	Years	BV/CV	FV/CV	total tissue/CV	bone/new tissue
1	rw	102	6	2	0.07	0.12	0.20	0.38
2	rw	cant measure	6	6	0.00	0.02	0.02	0.00
3	rw	346	20	4	0.07	0.10	0.17	0.44
4	c	339.8	18	4	0.00	0.08	0.08	0.01
5	c	288.8	20	3	0.11	0.24	0.35	0.32
6	rw	71.1	6	1	0.02	0.04	0.06	0.27
7	rw	89.4	6	11	0.11	0.03	0.15	0.76
8	c	cant measure	7	19	0.08	0.18	0.26	0.30
9	c	cant measure	20	10	0.08	0.24	0.33	0.25
10	c	166.7	unknown	6	0.05	0.14	0.19	0.26
11	c	321.1	20	24	0.32	0.18	0.51	0.64
12	c	333.9	22	17	0.15	0.05	0.20	0.77
13	c	441	22	0.42	0.01	0.10	0.12	0.10
14	rw	314.9	22	6	0.01	0.03	0.04	0.20
15	c	511.7	25	8	0.29	0.07	0.36	0.81

Rw=round window; c=cochleostomy; bv=bone volume; cv=cochlear volume; fv=fibrosis volume