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Changes in the Inner Ear Structures in Cystic Fibrosis Patients

Henrique F. Pauna, M.D.^{1,2}, Rafael C. Monsanto, M.D.^{1,3}, Natsuko Kurata, M.D.^{1,4}, Michael M. Paparella, M.D.^{1,5}, and Sebahattin Cureoglu, M.D.¹

¹Department of Otolaryngology, Head & Neck Surgery, University of Minnesota Minneapolis, MN, USA

²Department of Otolaryngology, Head and Neck Surgery, State University of Campinas/ UNICAMP, Campinas, São Paulo, Brazil

³Department of Otolaryngology and Head and Neck Surgery, Banco de Olhos de Sorocaba Hospital (BOS), Sorocaba, São Paulo, Brazil

⁴Tokyo Medical and Dental University, Tokyo, Japan

⁵Paparella Ear Head & Neck Institute, Minneapolis, MN, USA

Abstract

Objective—Although prolonged use of antibiotics is very common in cystic fibrosis (CF) patients, no studies have assessed the changes in both cochlear and peripheral vestibular systems in this population.

Methods—We used human temporal bones to analyze the density of vestibular dark, transitional, and hair cells in specimens from CF patients who were exposed to several types of antibiotics, as compared with specimens from an age-matched control group with no history of ear disease or antibiotic use. Additionally, we analyzed the changes in the elements of the cochlea (hair cells, spiral ganglion neurons, and the area of the stria vascularis). Data was gathered using differential interference contrast microscopy and light microscopy.

Results—In the CF group, 83% of patients were exposed to some ototoxic drugs, such as aminoglycosides. As compared with the control group, the density of both type I and type II vestibular hair cells was significantly lower in all structures analyzed; the number of dark cells was significantly lower in the lateral and posterior semicircular canals. We noted a trend toward a lower number of both inner and outer cochlear hair cells at all turns of the cochlea. The number of spiral ganglion neurons in Rosenthal's canal at the apical turn of the cochlea was significantly

Address correspondence to: Sebahattin Cureoglu, MD, Department of Otolaryngology, University of Minnesota, Lions Research Building, Room 210, Mayo Mail Code 2873, 2001 6th Street SE, Minneapolis, MN 55455 [cureo003@umn.edu], 612-626-9875.

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lower; furthermore, the area of the stria vascularis at the apical turn of the cochlea was significantly smaller.

Conclusions—Deterioration of cochlear and vestibular structures in CF patients might be related to their exposure to ototoxic antibiotics. Well-designed case-control studies are necessary to rule out the effect of CF itself.

Keywords

Cystic fibrosis; inner ear changes; antibiotics; vestibular cells; cochlear cells

1. INTRODUCTION

Cystic fibrosis (CF), an autosomal recessive hereditary disease, is common among the white population. It primarily affects exocrine gland function and the viscosity of mucous secretion. Overall, the median survival time for CF patients is around 30 years, but children born in the United States in 1990 are projected to live longer than 40 years [1]. In 1989, the CF transmembrane conductance regulator (CFTR) gene was identified in the long arm of chromosome 7; its mutations can result in abnormal chloride ion transport [1–3].

CF patients are often repeatedly treated with a long-term course of antibiotics. Given the known accumulation of toxic antibiotics in other organs after prolonged antibiotic treatment, it is likely that the perilymph of the inner ear (including the cochlea and vestibule) is also affected [4]. Yet, in CF patients, an untreated infection due to *Pseudomonas aeruginosa* can result in progressive lung damage (bronchiectasis), respiratory failure, and death [4, 5].

Despite the higher incidence of respiratory infections in CF patients, their incidence of otitis media in this population remains under debate; in fact, studies published in this regard show conflicting data [1, 6, 7]. Although hearing impairment is easily recognizable in these patients, the vestibular symptoms due to damage in the vestibular system are insidious and include vague dizziness, vertigo, or a light-headed sensation, constituting a diagnostic challenge to both pediatricians and otolaryngologists [5]. Only a few studies have included histologic evaluation of the vestibular end organs in patients exposed to ototoxic antibiotics [8, 9].

To the best of our knowledge, ours is the first study to analyze the changes in both inner ear structures (cochlea and vestibule) of CF patients exposed to a several types of antibiotics, as compared with a control group of patients with no history of ear disease or antibiotic use, looking for initial changes that may indicate clinical features of the patients.

2. MATERIALS AND METHODS

From our archived human temporal bone collection at the University of Minnesota, we selected specimens for this study from deceased donors with a clinical diagnosis of CF by positive sweat test (sweat chloride value above 60 mEq/L [1, 10]). Excluded were specimens from donors who had tumors affecting the ear; who had leukemia; who underwent irradiation of the head and neck, chemotherapy, or any otologic surgery; who had clinical otosclerosis or a systemic autoimmune disease; or whose temporal bones were affected by

processing artifacts. The final *CF group* (Table 1) included 12 specimens (from 5 males and 7 females); their mean age was 23.0 ± 11.88 years (range, 10 to 49 years). All 12 of them had a history of antibiotic use.

Our age-matched *control group* included 12 specimens from donors with no history of ear disease or antibiotic use; their mean age was 29.27 ± 14.87 years (range, 3 to 69 years).

Using light microscopy, 3 of the authors (HFP, RCM, NK) independently scrutinized the slides of the specimens; the authors were blinded to information such as the age, gender, or medical history of the temporal bone donor. Then, the results obtained by the 3 authors were compared and reevaluated by a 4th author (SG).

The specimens used in our study had previously been harvested during autopsy, fixed in 10% buffered formalin, decalcified with ethylenediaminetetraacetic acid, dehydrated in graded concentrations of alcohol, and embedded in celloidin. Each temporal bone was serially sectioned in the horizontal plane at a thickness of 20 μm . Every 10th section was stained with hematoxylin and eosin, then mounted on a glass slide.

2.1 Vestibular hair cells

To measure hair cell density, we scrutinized every 10th horizontal section of the maculae of the saccule and utricle, as well as of the cupulae of the lateral and posterior semicircular canals. Excluded from our analysis were the structures in the anterior semicircular canal: they are usually absent because of our processing routine, which involves horizontally cutting the temporal bones.

We distinguished vestibular hair cells on the basis of their morphologic features: type I cells have a round nerve chalice (giving these cells a piriform shape) and a spherical nucleus; type II cells do not have a nerve chalice, and both their external appearance and their nucleus are cylindrical.

To evaluate the density of type I and II hair cells, we used a differential interference contrast microscope (AxioCam, Carl Zeiss Microscopy, Pleasanton, CA, USA) at a magnification of $\times 1,250$. We individualized each hair cell type; then, using the criteria of Merchant, we counted cells with an identifiable nucleus that were within a width of 500 μm [11]. We corrected the raw hair cell density according to the formula of Abercrombie [12]. The final cell density was expressed as the number of cells per surface area of 0.01 mm^2 .

2.2 Dark cells

To compare the number of dark cells, between the 2 groups, in the crista ampullaris of the lateral and semicircular canals, we used light microscopy. We distinguished dark cells from transitional cells on the basis of their intensely stained (by hematoxylin and eosin) nuclei, located in the endolymphatic edge of each dark cell. Moreover, dark cells are intimately associated with melanin particles. We counted vestibular dark cells with an identifiable nucleus that were within 100 μm of the transitional epithelium [12]. The results were expressed as the number of dark cells per area within 100 μm of the transitional epithelium.

2.3 Transitional cells

We defined transitional cells as the cuboid cells that are between vestibular hair cells and dark cells. The nucleus of cuboid cells is in the middle of each cell. To evaluate them, we used the same specimen slide that we used to count the adjacent dark cells in the crista ampullaris of the lateral and posterior semicircular canals. The results were expressed as the number of transitional cells per area in the vestibular compartment.

2.4 Cochlear hair cells

To compare the cochlear hair cells in the midmodiolar section of the cochlea, we used light microscopy. We assessed the presence or absence of inner and outer hair cells in the organ of Corti at each turn of the cochlea (basal, medial, and apical). The results were expressed as the percentage of cochlear hair cell loss at each turn, as well as the total.

2.5 Spiral ganglion neurons

We also counted the number of spiral ganglion neurons in the midmodiolar section of the cochlea, again using light microscopy. For this step, we counted only the spiral ganglion neurons in Rosenthal's canal. The results were expressed as the number of spiral ganglion neurons in the canal at each turn of the cochlea (basal, medial, and apical), as well as the total.

2.6 Stria vascularis

To evaluate the area of the stria vascularis, we used a 64-bit Nikon Eclipse E400 imaging system equipped with measurement software (NIS-Elements Basic Research, version 4.30.01, Nikon, Instruments Inc., Tokyo, Japan). We measured the area of the stria vascularis at each turn of the cochlea (basal, medial, and apical). The results were expressed as the mean area (in μm^2) of each section and at each turn.

2.7 Statistical analysis

To calculate and compare the density of hair, dark, and transitional cells between the 2 groups and by donor gender, we used the Student *t* test for normally distributed data; the nonparametric Mann-Whitney U test, non-normally distributed data (SPSS 23.0 software for Windows, SPSS Inc., Chicago, IL). All results were expressed as the mean $\pm$ standard deviation (SD). Findings were considered statistically significant when the *P* value was less than 0.05.

3. RESULTS

Of the 12 specimens in the *CF* group, one (8.33%) had signs of effusion in the middle ear. Of those 12 specimens, 10 (83.33%) were from donors who were exposed to one or more aminoglycosides (e.g. gentamicin, tobramycin); however, information regarding the length of use for those antibiotics was not available in the medical charts. In addition, 8 (66.67%) of the 12 specimens in the *CF* group was from a donor who had a positive culture for *P. aeruginosa* in the sputum. Of the 6 donors in that group who underwent audiometry while

alive, 2 (33.33%) had hearing loss (as measured by pure-tone audiograms with hearing thresholds above 25 dB) involving frequencies above 2000 Hz (Fig. 1).

3.1 Vestibular hair cells

In the *CF group* (as compared with the *control group*), the density of type I hair cells was significantly lower in both the lateral (31.09 ± 7.63 vs. 45.81 ± 10.04 ; $P = 0.005$) and posterior semicircular canal (29.66 ± 8.8 vs. 45.63 ± 4.82 ; $P = 0.001$), in the saccule (25.8 ± 9.44 vs. 41.75 ± 7.25 ; $P = 0.0004$), and in the utricle (28.08 ± 4.56 vs. 43.25 ± 7.04 ; $P < 0.0001$). The density of type II hair cells was also significantly lower in the *CF group* in both the lateral (8.0 ± 3.79 vs. 16.81 ± 2.99 ; $P = 0.001$) and posterior semicircular canal (6.88 ± 1.9 vs. 16.45 ± 2.97 ; $P < 0.0001$), in the saccule ($P < 0.0001$), and in the utricle ($P < 0.0001$) (Fig. 2).

We searched the medical charts of the 12 donors who had CF for information regarding dizziness and/or vertigo. Of the 8 donors for whom such information was available, 6 did not experience vestibular symptoms. However, the other 2 had a history of vertigo; in both of them, vestibular tests demonstrated bilateral hypofunction of the vestibular system. When we compared those 2 subgroups (i.e., the 2 donors with vertigo vs. the 6 without), we found no statistically significant differences in the density of either type I or type II vestibular hair cells.

3.2 Dark cells

The mean number of dark cells in the lateral semicircular canal was significantly lower in the *CF group* (12.75 ± 3.62) than in the *control group* (16.81 ± 2.67) ($P = 0.021$). The mean number of dark cells in the posterior semicircular canal was also significantly lower in the *CF group* (14.0 ± 2.08) than in the *control group* (16.08 ± 2.57) ($P = 0.041$).

3.3 Transitional cells

The mean number of transitional cells in the lateral semicircular canal was 17.16 ± 3.63 in the *CF group*, 19.41 ± 2.39 , in the *control group* ($P = 0.087$). The mean number of transitional cells in the posterior semicircular canal was 18.58 ± 2.77 in the *CF group*, 20.0 ± 3.1 , in the *control group* ($P = 0.211$).

3.4 Cochlear hair cells

Of the 12 specimens in the *CF group*, 2 (16.67%) were compromised by fixation artifacts, so we were not able to evaluate the organ of Corti in these 2. In the *control group*, we observed hair cell loss in the organ of Corti in 6 specimens at the basal turn; in 6, at the medial turn; and in 4, at the apical turn. But the differences between the 2 groups were not statistically significant. The odds ratio of hair cell loss in the organ of Corti for the *CF group*, as compared to the *control group*, is shown in Table 2.

In the *CF group*, we observed *inner* hair cell loss in 7 of the specimens at the basal turn of the cochlea; in 4, at the medial turn; and in 7, at the apical turn. In the *control group*, we observed inner hair cell loss in 4 of the specimens at the basal turn; in 3, at the medial turn; and in 4, at the apical turn (Fig. 3).

In the *CF group*, we observed *outer* hair cell loss in 6 of the specimens at the basal turn; in 6, at the medial turn; and in 7, at the apical turn. In the *control group*, we observed outer hair cell loss in 4 specimens at the basal turn; in 6, at the medial turn; and in 4, at the apical turn.

3.5 Spiral ganglion neurons

The mean number of spiral ganglion neurons was 157.33 ± 80.34 , in the *CF group*, 193.25 ± 57.78 , in the *control group* ($P = 0.222$). The mean number in Rosenthal's canal at the basal turn of the cochlea was 42.25 ± 15.53 , in the *CF group*, 50.16 ± 17.19 , in the *control group* ($P = 0.249$). The mean number in Rosenthal's canal at the medial turn was 46.75 ± 19.31 , in the *CF group*, 53.25 ± 11.3 , in the *control group* ($P = 0.325$). The mean number in Rosenthal's canal at the apical turn was 74.54 ± 64.38 , in the *CF group*, and 94.83 ± 57.3 , in the *control group* ($P = 0.013$). We observed a statistically significant difference between the 2 groups *only* in the number of spiral ganglion neurons in Rosenthal's canal at the apical turn (Fig. 4).

3.6 Stria vascularis

The mean area of the stria vascularis at the apical turn of the cochlea was $5228.3 \pm 1779.16 \mu\text{m}^2$ in the *CF group*, lower than in the *control group* ($7569.43 \pm 1958.2 \mu\text{m}^2$) ($P = 0.013$) (Fig. 3). We also observed a statistically significant difference between the 2 groups in the overall mean area of the stria vascularis ($P = 0.028$). But we noted no statistically significant differences at the other turns between the 2 groups ($P = 0.104$, basal turn; $P = 0.077$, medial turn).

In terms of donor gender, we noted no statistically significant differences in any of the inner ear structures. Results and statistical analysis are shown in Table 3.

4. DISCUSSION

P. aeruginosa is among the most common organisms causing bacterial infections in CF patients. The antibiotic therapy in these patients usually include more than one class of drugs. Antipseudomonal beta-lactam penicillin or quinolones, in conjunction with aminoglycosides are usually necessary to treat these patients. But because of their narrow therapeutic window, those antibiotics can have a toxic effect on the kidney and on the inner ear structures. A clinical study with 23 CF patients (median age, 32.5 years) exposed to tobramycin, with their vestibular symptoms assessed per physical examinations and per electronystagmography with caloric irrigation reported a 30.4% prevalence rate of peripheral vestibular hypofunction and a 21.7% rate of bilateral hypofunction—suggesting that vestibulotoxicity was induced by the use of tobramycin [4]. Consistent with our histological findings, Zheng et al. [13] observed vacuolization of the sensory cells in the cristae, and in the striolar regions of the macula of the saccule, in a 25-year-old CF patient who died of respiratory insufficiency.

Many studies have assessed the audiologic changes, found by means of audiometric evaluation, in CF patients. The prevalence rate of hearing loss or abnormal hearing among CF patients ranges from 1% to 50.8% [7, 14–20]. However, those studies used different definitions of hearing loss, e.g., as measured by pure-tone audiograms with hearing

thresholds below 15 dB, as reported by patients themselves, as limited to high-frequency hearing loss, or as determined by diminished scores on word-recognition tests. We found similar prevalence among our patients (40%) considering hearing loss when hearing thresholds are lower as 25 dB.

Other previous studies have reported degeneration of spiral ganglion cells and cochlear hair cells in human temporal bones, as well as high-frequency hearing loss after exposure to aminoglycosides (intravenous or nebulized) [5, 13, 21–25]. In our study, we observed a decrease in the number of spiral ganglion neurons in Rosenthal's canal in temporal bone specimens from deceased donors with CF (as compared with our *control group*); however, such decrease was not correlated with a greater degree of hearing loss. We also demonstrated degeneration of the organ of Corti at all the turns of the cochlea (basal, medial, and apical), but that degeneration was not correlated with a greater degree of hearing loss.

A few human temporal bone studies have described segmental degeneration and/or atrophy of the stria vascularis in deceased donors who were exposed to gentamicin, tobramycin, neomycin, or kanamycin [22, 26, 27]. Similarly, in our study, we found a smaller stria vascularis, mainly at the apical turn, in our *CF group*. Because the cochlea is supplied by a single terminal artery, the labyrinthine artery, it becomes very susceptible to inner ear circulatory changes caused by aminoglycosides [23, 28].

We found degeneration of the inner and outer hair cells of the organ of Corti at *all* turns of the cochlea. In contrast, most studies of the ototoxic effects of aminoglycosides in the inner ear structures have described damage at, or beginning by, the basal turn [23, 27, 29].

The full reasons that antibiotics have a toxic effect on the inner ear structures of CF patients are unknown. Ototoxicity with sensorineural hearing loss due to aminoglycosides occurs at the level of cochlear hair cells secondary to the generation of reactive oxygen specimens [30]. Because hair cells at the basal turn of the cochlea are affected first, high-frequency hearing loss is one of the first findings, occurring as early as 4 hours after treatment [30]. Aminoglycoside toxicity might involve a genetic predisposition, at least as a contributing factor: several mitochondrial gene mutations in the MT-RNR1 and MT-TS1 groups (including the mitochondrial 1555A>G mutation) might be culpable [30–32], and many studies have compared the efficacy and toxic potential of different regimens of antibiotics in CF patients, with varying results [15, 20, 32–34].

In our study, human temporal bone specimens from donors with CF who were exposed to antibiotics (as compared with our *control group*) showed a significant loss of vestibular hair cells (both type I and II), dark cells, and spiral ganglion neurons in Rosenthal's canal at the apical turn of the cochlea, as well as a decrease in the area of the stria vascularis at the apical turn of the cochlea.

5. CONCLUSION

In our study, we found histopathologic changes due to exposure to ototoxic antibiotics—especially aminoglycosides—in both vestibular and cochlear structures of human temporal bone specimens from deceased donors with CF. We believe that deterioration of those

structures might be responsible for the clinical symptoms of dizziness and/or vertigo as well as hearing loss. Our results reinforce the necessity of rational use of antibiotics that follow strict treatment guidelines and protocols; plus, early referral to an otolaryngologist is needed, if possible as soon as the first symptoms arise. Well-designed case-control studies are necessary to rule out the effect of CF itself in both cochlear and peripheral vestibular structures.

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Abbreviations

CF cystic fibrosis

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Figure 1.

Top: Audiogram results of the right ear of a donor in the CF group. Bottom: Audiogram results of the left ear of these same donors.

Figure 2.

Histologic sections from an utricle, demonstrating the presence and/or absence of vestibular type I and type II cells (hematoxylin and eosin, magnification x 10). (A) the control group; (B) the CF group. Arrows are pointing to vestibular cells. Note the greater quantity of cells within the control section.

CF = cystic fibrosis

Figure 3.

Histologic sections of a cochlear duct from (A) the control group and (B) the CF group. Black arrow = stria vascularis; note its smaller area in (B), and the blue line reinforces the difference of the area of the stria vascularis. Hollow arrow = the organ of Corti; note how degenerate it is in (B) (hematoxylin and eosin, magnification x 10). The “*” shows the position and number of cochlear hair cells on each section.

Figure 4.

Midmodiolar section from (A) the control group and (B) the CF group, demonstrating the loss of spiral ganglion neurons in Rosenthal's canal in (B) (hematoxylin and eosin, magnification x 2). The hollow arrows point to the Rosenthal's canal in the control group with a greater number of spiral ganglions cells. The black arrows point to the Rosenthal's canal in the CF group.

Table 1

Epidemiologic characteristics of our CF group.

Donor No.	Age, y/Gender/Race	Family history of CF	Ear infection	Symptoms	Antibiotics used	Culture results
1*	7/M/white	NA	No	No	tetracycline	NA
2	11/M/white	NA	No	NA	dicloxacillin, sulfisoxazole, erythromycin, polymyxin, gentamicin, carbenicillin	NA
3	18/F/white	No	No	No	sulfamethoxazole, ampicillin, sulfamethoxazole and trimethoprim, gentamicin	<i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i>
4*	40/M/white	Yes	No	Tinnitus	doxycycline, tobramycin, ticarcillin, piperacillin, ampicillin, amikacin, ciprofloxacin	<i>Pseudomonas aeruginosa</i>
5*	21/F/white	NA	No	Dizziness (ENG normal but with hypofunction bilaterally)	tobramycin, piperacillin, sulfamethoxazole and trimethoprim, ceftazidime, vancomycin, chloramphenicol	<i>Pseudomonas cepacia</i>
6*	27/F/white	NA	No	Vertigo and tinnitus (ABR normal bilaterally, ENG with no function)	ceftizoxime, doxycycline, trimethoprim, nafcillin, tobramycin, ticarcillin, amoxicillin	<i>Pseudomonas cepacia</i> , <i>Pseudomonas aeruginosa</i> , <i>Serratia marcescens</i> , <i>Haemophilus influenzae</i> , <i>Aspergillus fumigatus</i>
7*	25/F/white	NA	No	NA	doxycycline, chloramphenicol, imipenem, tobramycin, sulfamethoxazole, clindamycin	<i>Pseudomonas aeruginosa</i> , <i>Candida</i>
8	20/F/white	NA	No	NA	tobramycin, imipenem, piperacillin, ciprofloxacin, aztreonam, Timentin, ceftazidime, tetracycline, Adriamycin	<i>Pseudomonas aeruginosa</i>
9	11/F/white	NA	NA	NA	ticarcillin, tobramycin, vancomycin, amphotericin B, itraconazole	<i>Pseudomonas aeruginosa</i> , <i>Streptococcus</i> , <i>Micrococcus</i> , <i>Aspergillus</i>
10	16/F/white	NA	No	No	tobramycin, ciprofloxacin, imipenem, fluconazole, chloramphenicol	<i>Pseudomonas aeruginosa</i> , <i>Aspergillus fumigatus</i>
11	28/M/white	NA	No	No	imipenem-tobramycin, Timentin-tobramycin, erythromycin, ciprofloxacin, ceftizoxime, aztreonam	<i>Pseudomonas aeruginosa</i>
12	49/M/white	NA	No	No	sulfamethoxazole and trimethoprim, itraconazole, Timentin	<i>Aspergillus fumigatus</i> , <i>Stenotrophomonas maltophilia</i>

* audiogram information available

ABR = auditory brain response; CF = cystic fibrosis; ENG = electronystagmography; F = female; M = male; NA = not available; No. = number; y = years

Table 2

Odds ratio of hair cell loss in the organ of Corti for the 2 groups.

	Odds ratio	95% CI	<i>P</i>
Inner basal	4.6667	0.765 – 28.4669	0.095
Outer basal	1.5	0.2747 – 8.1897	0.6396
Inner medial	2.0	0.3244 – 12.329	0.4551
Outer medial	1.5	0.2747 – 8.1897	0.6396
Inner apical	4.6667	0.765 – 28.4669	0.095
Outer apical	4.6667	0.765 – 28.4669	0.095

CI = confidence interval

Table 3

Characteristics of our findings within the structures that were analyzed.

	CF group	Control group	P value
Type I Vestibular			
Hair Cells (number of cells / 0.01 mm²)			
<i>Lateral SCC</i>	31.09 ± 7.63	45.81 ± 10.04	0.005
<i>Posterior SCC</i>	29.66 ± 8.8	45.63 ± 4.82	0.001
<i>Sacculle</i>	25.8 ± 9.44	41.75 ± 7.25	0.0004
<i>Utricle</i>	28.08 ± 4.56	43.25 ± 7.04	<0.0001
Type II Vestibular			
Hair Cells (number of cells / 0.01 mm²)			
<i>Lateral SCC</i>	8.0 ± 3.79	16.81 ± 2.99	0.0001
<i>Posterior SCC</i>	6.88 ± 1.9	16.45 ± 2.97	<0.0001
<i>Sacculle</i>	7.2 ± 2.78	16.33 ± 3.44	<0.0001
<i>Utricle</i>	8.25 ± 2.34	18.58 ± 3.26	<0.0001
Dark Cells (number of cells / 100 µm)			
<i>Lateral</i>	12.75 ± 3.62	16.81 ± 2.67	0.021
<i>Posterior</i>	14.0 ± 2.08	16.08 ± 2.57	0.041
Transitional Cells (number of cells / 100 µm)			
<i>Lateral</i>	17.16 ± 3.63	19.41 ± 2.39	0.087
<i>Posterior</i>	18.58 ± 2.77	20.0 ± 3.10	0.211
Spiral Ganglions Cells (number of cells)			
<i>Total</i>	157.33 ± 80.34	193.25 ± 57.78	0.222
<i>Basal turn</i>	42.25 ± 15.53	50.16 ± 17.19	0.249
<i>Middle turn</i>	46.25 ± 19.31	53.25 ± 11.3	0.325
<i>Apical turn</i>	74.54 ± 64.38	94.83 ± 57.3	0.013
Stria Vascularis (mean, in mm²)			
<i>Basal turn</i>	9452.69 ± 1601.49	10452.63 ± 1888.24	0.104
<i>Middle turn</i>	6969.0 ± 1125.79	8142.75 ± 1881.34	0.077
<i>Apical turn</i>	5228.3 ± 1779.16	7569.43 ± 1958.2	0.013

CF = cystic fibrosis, SCC = semicircular canal