Table I. Patients and surgical procedures.

Surgical procedure	*n*	Disease/condition	*n*
Tympanoplasty	48	Cholesteatoma	20
		Chronic otitis media	22
		Malformation of auditory ossicles	5
		Transaction of auditory ossicles	1
Cochlear implant	11	Deafness	11
Exploratory tympanotomy	4	Perilymphatic fistula	3
		Temporal bone fracture	1
Stapes surgery	3	Otosclerosis	2
		Foreign body in middle ear	1
Translabyrinthine removal of vestibular schwannoma	2	Acoustic tumor	2
Canal plugging	1	Benign paroxysmal positional vertigo	1
Partial removal of temporal bone	1	Middle ear tumor	1
Removal of external ear osteoma	1	External ear osteoma	1

The SVV was measured by means of a small rotatable luminous line in the upright body position in a completely darkened room. The patient was seated in front of the SVV device. After the luminous line was tilted automatically, the subject was asked to rotate the bar to the position they felt vertical using a hand controller. The SVV measurement was performed 10 times for each subject and its mean value was regarded as the measured value. In this study, we designated tilting of the SVV toward the operated side as negative, and tilting to the healthy side as positive. SVV was tested preoperatively and postoperatively to investigate any direction changes. In most patients, SVV was measured on postoperative day 1, but in a few patients who required bed rest it was tested a few days after the surgery.

Postoperative positional nystagmus was recorded with an infrared CCD camera. We measured SVV in 21 healthy volunteers, in whom the mean ± SD of SVV was 0.05 ± 0.73. Based on this result, the upper limit of the normal range was set as ±2.0° and tilts greater than −2.0° to +2.0° were determined to be pathologic [7].

We classified the patients into three groups by the deviation value of SVV as deviation toward the healthy side, deviation toward the operated side, and no deviation (SVV <2.0°). We designated the patient with preoperative pathologic SVV and postoperative normal SVV as deviation toward the healthy side and the patients with both preoperative and postoperative pathologic SVV as no deviation.

Results

Tympanoplasty (48 patients) (Figure 1)

Postoperative SVV tilted to the healthy side in 18 patients (37.5%), to the operated side in 3 (6.2%), and there was no deviation in 27 (56.3%) (Table II). There was significant change of SVV between the preoperative and postoperative values ($p = 0.0003$, Wilcoxon test). Postoperative positional nystagmus was observed in nine patients (18.8%); toward the operated side in seven and toward the healthy side in two (Table III). There were no obvious differences in the results of the SVV tilt according to the types of tympanoplasty.

Cochlear implant (11 patients) (Figure 2)

Postoperative SVV tilted to the healthy side in four patients (36.4%), to the operated side in one patient (9.1%), and there was no deviation in six patients (54.5%) (Table II). There was no significant difference in the SVV values. Postoperative nystagmus toward the operated side was observed in four patients and to the healthy side in one (Table III).

Exploratory tympanotomy (four patients) (Figure 3)

Postoperative SVV tilted to the healthy side in one patient (25.0%) and there was no deviation in three patients (75.0%) (Table II). Postoperative positional nystagmus toward the operated side was observed in two patients (Table III).

Stapes surgery (three patients) (Figure 3)

Postoperative SVV tilted to the healthy side in all patients. The postoperative SVV was significantly different from preoperative SVV ($p = 0.0495$, Mann-Whitney U test). Postoperative nystagmus toward the operated side was observed in two patients (Table III).

Translabyrinthine removal of vestibular schwannoma (two patients) (Figure 3)

Postoperatively SVV tilted to the lesion side and postoperative positional nystagmus toward the healthy side was observed in two patients (Tables II and III).

Other ear surgeries (Figure 3)

The postoperative SVV tilted to the healthy side in patients with canal plugging for benign paroxysmal

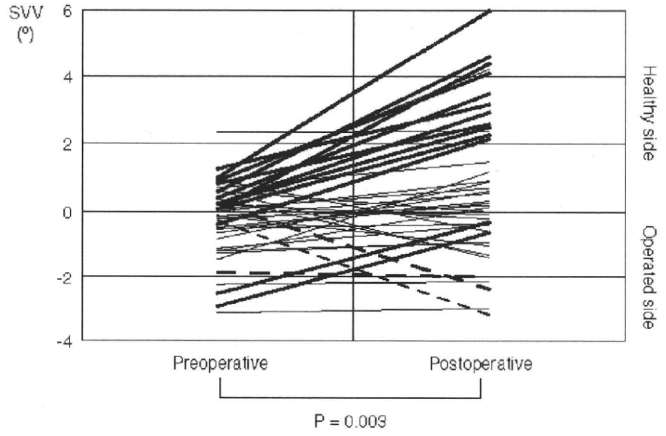

Figure 1. Preoperative and postoperative SVV changes following tympanoplasty in 48 patients. The solid thick line indicates the SVV shift to the healthy side, the solid thin line indicates no deviation, and the dotted line indicates the SVV shift to the operated side. Positive values in this figure represent the deviation toward the healthy side.

positional vertigo (BPPV). There were no pathologic SVV deviations in patients with removal of external ear osteoma and removal of the temporal bone. In the patient with BPPV, the positional nystagmus was directed toward the operated side in the 5 days postoperatively, but the direction of the nystagmus changed to the healthy side later. On the other hand, the postoperative SVV remained tilted to the healthy side. In the patients with removal of the temporal bone, the nystagmus was toward the healthy side. Preoperative and postoperative SVV results are summarized in Table II.

Discussion

The SVV test in upright body position is a simple and quick otoneurological test that provides information on the tonic afferent balance between the otolithic organs [8]. The SVV test result might indicate an otolithic disorder, in the same way that spontaneous nystagmus reflects the semicircular canal afferent balance [9]. Ear surgery has an influence not only on the otolith organs but also on the semicircular canals. In the patients with translabyrithine removal of vestibular schwannoma who had a spontaneous nystagmus, we speculate that semicircular canal and otolithic influences had affected the severe deviation of postoperative SVV. However, most patients in this study did not have spontaneous nystagmus, but had positional nystagmus or pathologic SVV shift. In these patients, we cannot completely rule out the influence of the semicircular canals, but we speculate that the otolithic condition mainly affected the postoperative

Table II. Preoperative and postoperative SVV ranges and postoperative direction of SVV tilting.

Surgical procedure	No. of patients	Range of preoperative SVV deviation (mean value)	Range of postoperative SVV deviation (mean value)	Postoperative SVV direction change		
				To the operated side	To the healthy side	No change
Tympanoplasty	48	3.14° to 2.32° (0.24°)	3.22° to 6.01° (0.86°)	3 (6.2%)	18 (37.5%)	27 (56.3%)
Cochlear implant	11	2.22° to 1.52° (0.25°)	8.72° to 5.30° (0.03°)	1 (9.1%)	4 (36.4%)	6 (54.5%)
Exploratory tympanotomy	4	3.58° to 3.11° (1.21°)	2.39° to 2.21° (0.06°)	0	1 (25%)	3 (75.0%)
Stapes surgery	3	0.10° to 1.33° (0.84°)	5.96° to 6.93° (6.32°)	0	3 (100%)	0
Translabyrinthine removal of vestibular schwannoma	2	0.05° to 0.69°	13.7° to 8.76°	2 (100%)	0	0
Canal plugging	1	2.38°	7.72°	0	1	0
Partial removal of temporal bone	1	0.17°	1.03°	0	0	1
Removal of external ear osteoma	1	0.27°	1.99°	0	0	1

Table III. Occurrence of postoperative nystagmus and pathologic SVV shift (greater than 2° to 2°).

Surgical procedure	Rate of positional nystagmus	Nystagmus		Deviation of SVV	
		Direction	*n*	Side	*n*
Tympanoplasty	9/48 (18.8%)	Operated side	7	Healthy side	3
				Operated side	2
				No deviation	2
		Healthy side	2	Healthy side	1
				No deviation	1
		No nystagmus	38		
Cochlear implant	5/11 (45.5%)	Operated side	4	Healthy side	2
				No deviation	2
		Healthy side	1	Operated side	1
		No nystagmus	6	Healthy side	2
				No deviation	4
Exploratory tympanotomy	2/4 (50%)	Healthy side	2	No deviation	2
		No nystagmus	2	Healthy side	1
				No deviation	1
Stapes surgery	2/3 (66.6%)	Operated side	2	Healthy side	2
		No nystagmus	1	Healthy side	1
Translabyrinthine removal of vestibular schwannoma	2/2 (100%)	Healthy side	2	Operated side	2
Canal plugging	1/1 (100%)	Operated side	1	Healthy side	1
Partial removal of temporal bone	1/1 (100%)	Healthy side	1	No deviation	1

deviations of SVV when absence of spontaneous nystagmus is considered.

It has been reported that vibration is an excitatory stimulus for semicircular canal and otolith afferents, and the net effect of an oscillating mechanical stimulus delivered to the hair bundle of a vestibular receptor cell is excitatory [10]. Vibration to the surface of the bony labyrinth using a conventional surgical drill dislodges the otoconia from the utricle [11] and it is suggested that the use of the surgical drill affects the otolithic organs. It was reported that the utricular nerve has monosynaptic and disynaptic connection with the abducens motoneurons and also has polysynaptic connections with the inferior oblique and trochlear motoneurons [12]. In the otolithic organ, the utricular nerve potentially affects SVV more than the saccule [13,14]. Polysynaptic connections between the utricular nerve and the inferior oblique and trochlear motoneurons seemed to play a role in eye rotation during head tilt [12], and hence we speculate that these nerves also contribute to the SVV deviations. In this study, we investigated the influence of ear surgery on otolithic function by measuring the SVV in the upright position. In previous studies, the significant tilting of the SVV to the lesion side had been described in patients with peripheral vestibular disorders including labyrinthectomy [1 6]. Postoperatively, SVV in an upright position tilted toward the operated ear in patients with vestibular neurectomy or cochleo-vestibular neurectomies [2 6]. These abnormalities in vertical perception are due to changes in the afferent gravioceptive pathways in the vestibular nerve. In this study, the SVV also tilted toward the operated side after translabyrithine removal of vestibular schwannoma. However, in other ear surgeries, the SVV tended to tilt toward the healthy side.

Tribukait and Bergenius [7] reported that in the acute stage after stapedotomy, subjective visual horizontal (SVH) in an upright position significantly tilted toward the healthy side, and these results indicate an increase in the resting activity of the utricular afferent nerve. In this study, SVV of all patients with stapes surgery tilted to the healthy side and postoperative nystagmus toward the operated side was observed in two patients. Stapes surgery opening the vestibule may have caused slight local labyrinthitis and irritation of the adjacent sensory structures, especially of the otolithic organs, leading to increase in the resting activity of the utricular afferent nerve.

Dizziness after cochlear implant surgery is a potential complication. Opening the labyrinth and inserting

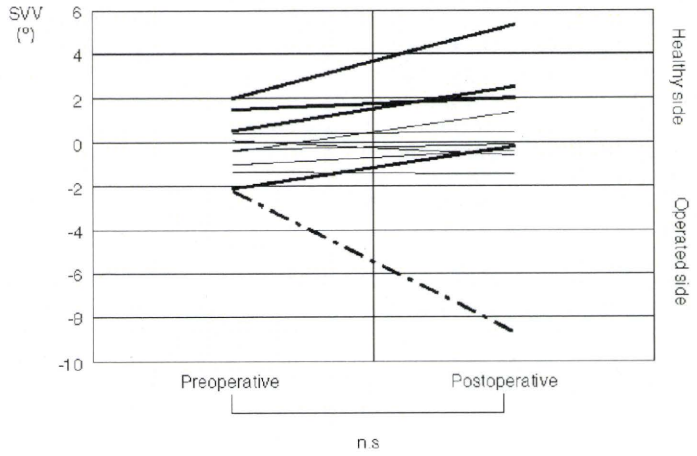

Figure 2. Preoperative and postoperative SVV changes following cochlear implant in 11 patients. The solid thick line indicates the SVV shift to the healthy side, the solid thin line indicates no deviation, and the dotted line indicates the SVV shift to the operated side. Positive values in this figure represent the deviation toward the healthy side.

the electrode after cochleostomy cause acute transient labyrinthitis. Temporal bone studies have shown that electrode insertion into the scala vestibule damages the osseous spiral lamina, basilar membrane, and vestibular receptors [15,16]. However, cochlear implant surgery does not always induce dizziness. In this study, the SVV tilted to the healthy side in four patients (36.4%), but it tilted to the operated side in one patient and postoperative positional nystagmus was observed in five patients. The mean values of postoperative SVV were smaller than those for stapes surgery and canal plugging. We assume that the cause of the small value change is due to the inner ear functions of the cochlear implant patients impaired preoperatively. The SVV of the other patient shifted markedly to the operated side and had a nystagmus toward the healthy side. The occurrence of severe inner ear damage was suspected in this case and the severity of vestibular function was speculated with the degree of SVV deviation.

In patients with a refractory posterior canal type BPPV, plugging of the posterior canal was performed using a transmastoid approach. Postoperatively the persistent positional nystagmus disappeared. The

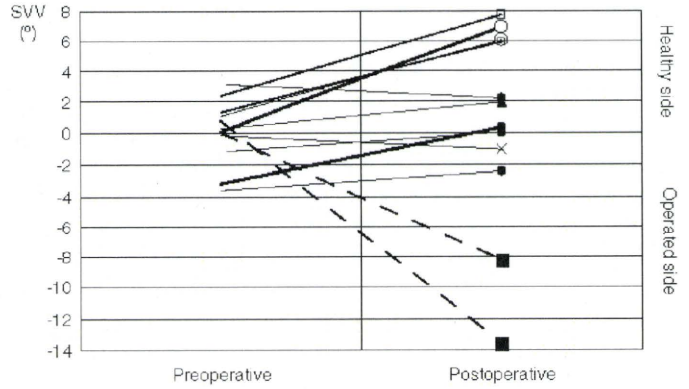

Figure 3. Preoperative and postoperative SVV changes with other surgeries in 12 patients. There was significant change of SVV between the preoperative and postoperative SVV in patients with stapes surgery. The solid thick line indicates the SVV shift to the healthy side, the solid thin line indicates no deviation, and the dotted line indicates the SVV shift to the operated side. Positive values in this figure represent the deviation toward the healthy side. ■, translabyrithine removal of vestibular schwannoma; ○, stapes surgery; ▲, removal of external ear osteoma; □, canal plugging; ●, exploratory tympanotomy; x, partial removal of temporal bone.

patient suffered a mild hearing loss temporarily but it soon improved. SVV tilted to the healthy side for 2 months after operation. Temporary hearing impairment was reported in previous studies [17,18] and it seemed to be due to an effect to the inner ear caused by the disrupted membranous labyrinth. Canal plugging slightly affects cochlear function, but also increases the resting activity of the utricular afferent. These results indicate that inner ear fenestration, such as stapes surgery, cochlear implant, and canal plugging activate the utricular afferents. However, other ear surgeries apart from inner ear fenestration also tend to move the SVV to the healthy side.

After tympanoplasty, the SVV of most patients shifted to the healthy side, as inner ear fenestration. In these cases the postoperative shift may be due to manipulation of the auditory ossicles or the ambient structures, or the effects of the surgical drill, or both. Not only tympanoplasty type III or IV requiring manipulation of stapes but also type I tympanoplasty cause the pathologic SVV. In patients undergoing tympanoplasty, postoperative SVV tilted to the operated side in three patients (6.2%), and their SVV ranged from 2.02° to 3.22°, two of them had postoperative nystagmus and had dizziness. The nystagmus direction was toward the operated side and no patient had any hearing impairment after surgery. It is suspected that the SVV results indicated the damage of the utriculus in these patients, but the damage did not include the cochlear function.

The patients with pathologic SVV did not always have postoperative nystagmus and the directions of the SVV tilt were not consistent with the direction of the nystagmus, and some of the patients with no nystagmus showed pathologic SVV deviation. These results indicate that the origin of the postoperative positional nystagmus and the postoperative SVV tilt are different.

In the patient with partial removal of temporal bone for external canal carcinoma, there was only a slight SVV deviation after the operation, probably because the vestibular organ was preserved. In this study, deviated postoperative SVV was normalized afterwards in almost all patients, including those who underwent translabyrithine removal of vestibular schwannoma. Ushio et al. [19] reported on long-lasting deviation of the SVH in patients with definite unilateral vestibular deafferentation and suggested the resection of the vestibular ganglion cells to be a contributory factor.

Disequilibrium is one of the most important complications following ear surgery. Postoperative nystagmus is an important indicator of disequilibrium. The SVV test in an upright body position can contribute to assessment of the otolithic dysfunction in a short time without complex equipment. Measurement of postoperative SVV seems to be an important clinical parameter to evaluate vestibular function such as observation of postoperative nystagmus.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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ORIGINAL ARTICLE

Morphological change of the cupula due to an ototoxic agent: A comparison with semicircular canal pathology

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Abstract

Conclusion: The cupula shows various degrees of changes after gentamicin (GM) injection into the inner ear, with or without damage of the sensory cells. This cupula change may be a part of the etiology of peripheral vertigo, and is also potentially one of the mechanisms of reduced caloric response. *Objectives:* To observe the morphological changes of the cupula after injecting GM in the frog inner ear and to compare the changes of the cupula with those of the ampullary sensory cells. *Methods:* We injected 300 μg (7.5 μl) of GM into the inner ear of 30 bullfrogs (Rana catesbeiana) using a microsyringe under ether anesthesia. The same amount of saline was injected into the other ear as control. The cupulae were observed at 3, 7, and 14 days after GM injection by stereoscopic microscope. The ampullae were fixed, and the sensory cells were assessed using a scanning electron microscope (SEM). The correlation between the changes in the cupula and sensory cells was evaluated using our own scale. *Results:* In over half of the cupulae in the 7- and 14-day groups, cupula changes such as shrinkage were observed. In about 50% of the total cases, the degree of cupula and sensory cell change correlated in the two groups. In the 14-day group, these changes were more marked. However, there were cases in which the changes of the cupula and sensory cells did not correlate, indicating that the cupula alone can sustain changes without sensory cell damage.

Keywords: *Gentamicin, ototoxicity, posterior semicircular canal, sensory cell, supporting cell*

Introduction

The effect of ototoxic drugs on the cochlea has been studied extensively. However, there are very few reports about disorders of the cupula, since it is fragile and morphologic evaluation is difficult. Suzuki et al. stained a cupula with India ink and observed its form and movement within the semicircular canal ampulla [1]. The semicircular canal responses change when the cupula is removed or cut in half. The semicircular canal activity can easily be modified by changes of the cupular morphology.

Regarding the effects of ototoxic agents on the inner ear, many studies have focused on the cochlea. However, most of them dealt with sensory cells, and there are few studies on the appendicular part of the sensory organ, such as the tectorial membrane. As for the vestibular appendages, there are studies on the otolith and otolithic membrane, but there are no detailed reports about the cupula. It is expected that if the cupula sustains morphological change, semicircular activity can be changed or dizziness may develop.

In this study, we examined the changes of the cupula that occurred after injecting gentamicin (GM) into the inner ear and compared the degree of the cupular changes with the changes of the ampullary sensory cells.

Material and methods

We used 30 bullfrogs (Rana catesbeiana). Under ether anesthesia, a small incision was made in the palate mucosa to identify the bony labyrinth. A microsyringe needle was inserted into the perilymphatic space to inject 300 μg (7.5 μl) of GM. The same amount of saline (7.5 μl) was injected into the other ear as a control.

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Table I. Evaluation of changes in cupula and sensory cells.

Cupula change	
Grade 1: Normal or limited change (ex. indentation of apex)	
Grade 2: Under 50% shrinkage	
Grade 3: 51 - 80% shrinkage	
Grade 4: More than 80% shrinkage or absence	

Sensory cell damage	
Grade 1: Lower than 20%	
Grade 2: 21 - 50%	
Grade 3: 51 - 80%	
Grade 4: More than 80%	

Observation of the cupula

The bullfrogs were divided into three groups, killed at 3, 7, or 14 days after GM injection; 10 frogs were used for each group. Under ether anesthesia, they were decapitated, and the cupula of the posterior semicircular ampulla was removed in Ringer's solution. The cupula was observed with a stereoscopic microscope after staining with India ink.

We classified cupula changes into grades 1–4 according to the degree of cupula shrinkage. Grade 1 is normal or slight change of the cupula such as the dip of the apex. Grade 2 is under 50% and grade 3 is 51– 80% of cupula shrinkage. Grade 4 is more than 80% of shrinkage or absence of the cupula (Table I).

Observation of the sensory epithelia

After removing the cupula, the sensory cells of the posterior semicircular canal were immediately fixed with 2.5% glutaraldehyde solution. Then conductive staining was performed with 1% osmium, before the sensory epithelium was dehydrated in a series of ethanols. Then, the isoamyl acetate was substituted for ethanol, before CO_2 critical point drying was performed. We observed the sensory cells with a scanning electron microscope (HITACHI S-800, SEM) after performing ion spattering coating with platinum palladium.

We classified the sensory cell changes into grades 1–4 according to the extent of sensory cell damage. Grade 1 is damaged sensory cell area smaller than 20% of the total area. Grade 2 is damage of 21–50%, grade 3, 51– 80% and grade 4, more than 80% (Table I).

In each group, the degree of the cupula change was compared with the changes in the sensory cells.

Results

The cupulae presented various kinds of changes after the GM injection. The main change was shrinkage starting from its margins, including the apex of the cupula (Figure 1).

Changes at 3 days after GM injection (Table II)

Normal or slightly changed cupulae (grade 1) were seen in 7 of 10 cases. Grade 4 change, disappearance of the cupula, was found in three cases. In these cases, the sensory cell change was also severe. Sensory cell changes were grade 2 or more severe in seven cases.

Changes at 7 days after GM injection (Table III)

The cupula showed mild changes of grade 2 or less in 5 of 10 cases. The sensory cells also showed mild changes of grade 2 or less (Figure 2). In the other five

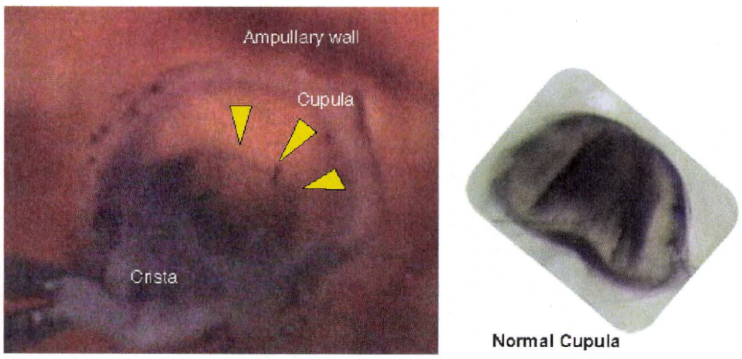


Figure 1. Cupula, grade 3: the cupula shrank from its apex side.

Table II. Relationship between changes in the cupula and sensory cells in the 3-day group ($n = 10$).

Cupula change \ Degree of sensory cell damage	1	2	3	4
1	2	2	3	
2				
3				
4		1	1	1

N = 10

cases, the degree of cupula change was not associated with the sensory cell change. In this group, the sensory cell change was no more severe than that in the 3-day group.

Changes at 14 days after GM injection (Table IV)

The cupula showed grade 2 or more severe changes in 7 of 10 cases. There were only two cases in which the cupula and sensory cell changes were both grade 2 or milder. In three cases, both the cupula and sensory cells had damage that was grade 3 or more (Figure 3). The other four cases showed no correlation between the cupula and sensory cell damage (Figure 4).

Control group

The cupula and sensory cells were normal in all six cases.

Table III. Relationship between changes in the cupula and sensory cells in the 7-day group ($n = 10$).

Cupula change \ Degree of sensory cell damage	1	2	3	4
1	2	1		3
2	1	1		
3				
4	1	1		

N = 10

Discussion

We set out to discuss the morphological changes of the cupula after injecting GM in the inner ear and to compare the changes of the cupula with those of the ampullary sensory cells.

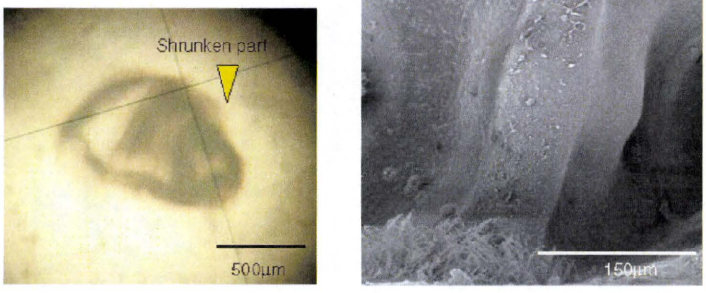
Regarding the effects of ototoxic agents on the inner ear, many studies have focused on the cochlea. However, most of them dealt with sensory cells, and there are few studies on the appendicular part of the sensory organ. Regarding cochlear appendages, disorder of the tectorial membrane was reported and is regarded to be a possible cause of hearing loss. For example, acoustic trauma and the 26 Connexin mutation, the DFNA8/12 family, and the β-tectorin mutation cause detachment of tectorial membrane from the sensory hair cells, rolling-up, and collagen fiber disorders, respectively [2 4]. As for the vestibular appendages, there are studies on the otolith and otolithic membrane, but there are no detailed reports about the cupula.

When we consider the morphological vulnerability of the cupula, we can imagine that the cupula easily sustains damage due to various insults. In this study, we observed the changes in the cupula and semicircular canal sensory cells after injecting GM into the inner ear. As a result, we observed damage of sensory cells as well as damage of the cupula, such as reduction of its size.

Morphologically, the cupula consists of small tubular structures and net-shaped structures filling the space among tubular structures [5]. Its biochemical component is mucopolysaccharides secreted from ampullary supporting cells. Also, innumerable pores are found at the bottom of the cupula, and sensory hairs grow into them [6,7].

In this study, after injecting GM, the cupulae always showed apical indentation while their bottom part remained intact (Figure 1). We readily confirmed this shrunken reduction of the cupula by staining it with India ink, which entered the space between the indented and shrunken cupula top and the ampullary roof. It was reported that the cupula is metabolized and maintained from the bottom, in the same way as the otolith organs. The mucopolysaccharide secreted by supporting cells supplies the cupula [8]. We assume that this is why the cupula always shrank from the apex.

It is expected that the movement of the cupula will change as it reduces in size. The normal cupula is suggested to seal the amupullary wall, thus separating the endolymph into two compartments. With physiological endolymphatic flow caused by head turning, the cupula bottom moves. As the quantity of endolymphatic flow increases, the central part of



Grade 2 Grade 2

Figure 2. Cupula and sensory cells 7 days after injecting gentamicin.

the cupula acts as a diaphragm [9–11]. Furthermore, when non-physiologically large flow occurs, the cupula starts to move much more like a swing-door due to dissociation between the cupula margin and the ampullary roof [12].

When the cupula shrinks, a gap is created between it and the ampullary wall. In this condition, the endolymphatic flow effect decreases because the endolymph passes through the gap [13] (Figure 5), thus possibly resulting in canal paresis (CP) of the caloric response even if the sensory cell function is normal. The shrunken cupula may lead to vestibulo-ocular reflex (VOR) delay in response to physiological stimulation. Under these conditions, unstable or floating symptoms during head movement may occur.

Table IV. Relationship between changes in the cupula and sensory cells in the 14-day group (n – 10).

Cupula change \ Degree of sensory cell damage	1	2	3	4
1		1	1	1
2	1			1
3				2
4	2			1

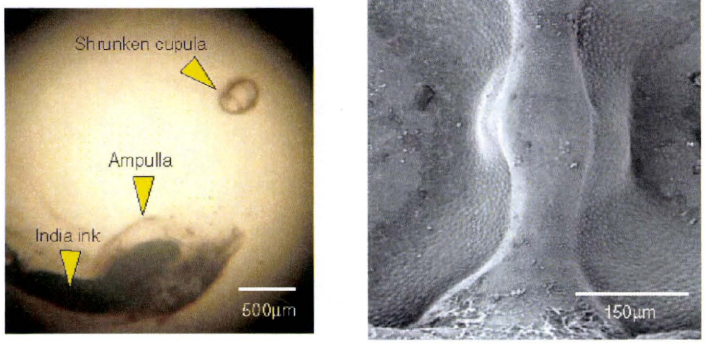
N = 10

Also, when cupulolithiasis occurs in the shrunken cupula, intense nystagmus could develop due to increased cupula flexibility. In this case, intensive positional nystagmus will be observed with the caloric CP. Generally, it is agreed that caloric CP indicates sensory cell or neural functional disorder. However, CP is also expected to occur when the cupula shrinks. Our results showing markedly shrunken cupula with mild sensory cell change support this concept.

Furthermore, reduction of the cupula size also may explain why semicircular canal plugging becomes ineffective in some cases [14,15]. Even if the distal end of the semicircular canal is plugged, the closed space effect between the plugging site and the cupula is abolished due to the space between the cupula and ampullary wall, thus leading to swing-door cupula movement and nystagmus.

In Meniere's disease, endolymphatic hydrops distends the ampullary wall, thus creating a gap between it and the cupula. This may also result in caloric CP. In benign paroxysmal positional vertigo (BPPV), it is possible that moving otoliths pass through the ampulla via this gap. Thus, a gap between the cupula and the ampullary wall makes the clinical picture of Meniere's disease and BPPV more complicated. We should be aware of cupular abnormalities when we make a diagnosis of vertigo.

Comparing the cupular change with sensory cell damage induced by GM injection, after 3 days 70% of cases showed normal cupulae, but sensory cell

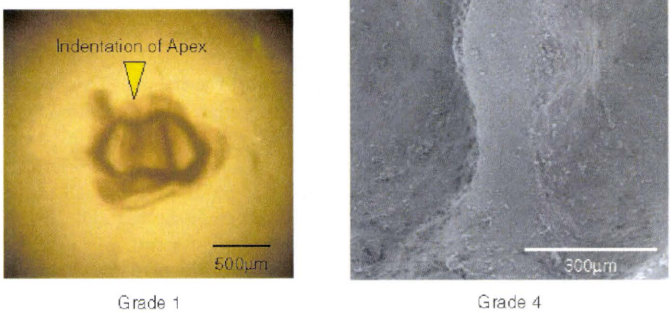


Grade 3 Grade 4

Figure 3. Cupula and sensory cells 14 days after injecting gentamicin.

changes of more than middle grade reached 80%. The sensory cells showed fusion and bulging of cilia, which seem to be the process toward hair cell collapse. In the 7- and 14-day groups, these ciliary changes were rarely seen, but instead more severe changes were seen. In the other 30%, the cupulae had disappeared and sensory cells were severely damaged, suggesting that these cases were highly sensitive to GM. In the 7-day group, mild cupula change was observed; 40% of cases exhibited grade 1 or grade 4 damage of the cupula and sensory cells that were not related to each other. In the 14-day group, grade 4 sensory cell disorder increased to 50%, and 80% of these showed cupular changes. Nevertheless, there were 30% of cases in which both the cupula and sensory cells were severely affected, but in another 30% of cases they were dissociated. This dissociation had not been predicted before.

Putting the data for the 20 animals in the 7- and 14-day groups together, 55% of them showed cupular change of grade 2 or more. Sensory cell change of grade 2 or more was observed in 70% of these cases, showing that the sensory cells changed more rapidly than the cupulae. The number of cases with both



Grade 1 Grade 4

Figure 4. Cupula and sensory cells 14 days after injecting gentamicin.

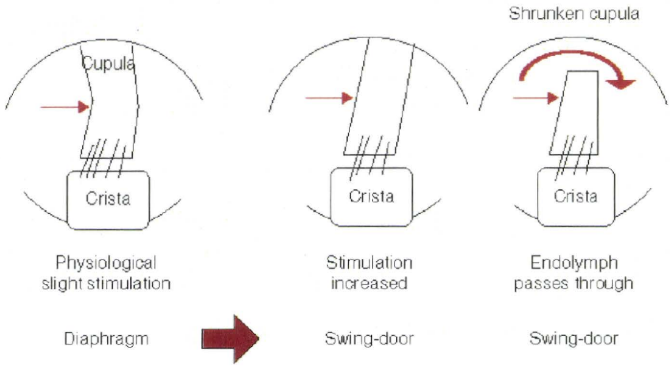


Figure 5. Change in the cupula movement due to shrinkage.

cupula and sensory cell damage was greater than in the 3-day group (Table V).

The toxic effect of GM on the sensory cell is greatest for type I sensory cells, followed by type II sensory cells, and supporting cells [16]. Bullfrogs have only type II sensory cells. However, our study also suggests that the frog sensory cells are more susceptible than supporting cells, since in the 7- and 14-day groups the sensory cell damage was more severe than the damage to the cupula, metabolism of which is mainly maintained by the supporting cells.

For maintenance of the sensory cells, the environment surrounding them plays an essential role. Therefore, not only the condition of the supporting cells but also the condition of neighboring cells and the ionic environment influence the cupula metabolism [17]. Also, sensory cells are protected by mucopolysaccharides produced from supporting cells. As supporting cell damage becomes more severe, denaturing and extinction of sensory cells would accelerate due to decrease of mucopolysaccaride protection. However, it is suggested that sensory cells do not always contribute to the cupula maintenance, since some cases with severely damaged sensory cells had normal cupulae. In cases with severely damaged cupulae and normal sensory cells, it is necessary to investigate the condition of the supporting cells. Also, how the cupula is reproduced is another issue to study.

Table V. Relationship in the 20 cases in the 7- and 14-day groups.

Cupula change \ Degree of sensory cell damage	1	2	3	4
1	2	2	1	4*
2	2	1		1
3				2
4	3*	1		1

N = 10

* Cases that displayed dissociation between the cupula and sensory cell change.

Generally, amphibians have high regenerative potential for sensory cells and nerves. Their membranous labyrinth is tough and resistant to mechanical insult [18,19]. The mammalian vestibular system is more vulnerable than that of amphibians. It is easy to speculate that the human cupula sustains more change than that of the frog as we observed in the present study.

If the cupula changes during or after an inner ear disorder, such as vestibular neuritis or Meniere's disease, it might be involved in the pathology of dizziness. This cupular change may also modify the clinical picture of positional vertigo [20]. We need to pay more attention to disorders of the appendicular part of the sensory organs as a possible lesion of peripheral vertigo.

Conclusions

(1) Cupula reduction started from its periphery after GM injection into the inner ear. (2) Changes in the cupula progressed for 2 weeks after GM injection. (3) There were cases in which the degrees of change in the cupula and sensory cells were dissociated. (4) Morphological changes of the cupula may be involved in the pathology of peripheral vertigo. (5) It is necessary to reconsider the mechanism of CP of the caloric response.

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ORIGINAL ARTICLE

Effect of cupula shrinkage on the semicircular canal activity

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Abstract

Conclusion: With half-sized cupula, the semicircular canal nerve potentials decreased under slow stimulus, thus potentially leading to reduced caloric response. This also suggests that shrunken cupula may cause dizziness because of its hypermobility. *Objectives:* To examine the physiological effect of half-sized cupula on the semicircular canal nerve potential. *Methods:* The isolated cupula of the bullfrog was sectioned in half with fine scissors and was replaced on the crista. Mechanical endolymphatic flow and slow and fast stimuli were delivered and the evoked action potentials were recorded. *Results:* The cupula was successfully sectioned in half and was replaced on the crista. With the half-sized cupula, the action potentials became smaller under slow stimulus than under fast stimulus.

Keywords: *Cupula replacement, caloric response, dizziness*

Introduction

The cupula plays an important role as a mechano-transducer of the semicircular canal (SC) receptor. However, studies on the cupula are scarce, because of its morphological vulnerability to chemical and mechanical insults. In a previous experiment using gentamicin we found that the cupula shrinks from the margin, leaving the part facing the sensory epithelia intact [1]. Shrinkage of the cupula may result in decrease in endolymphatic fluid shift and hypermobility of the cupula, leading to reduced caloric response and dizziness, respectively. There are some reports on physiological differences in SC activity between the caloric test and quick head rotation test [2 4]. This difference has been suggested to be due to activation of different sensory cell groups that are sensitive to slow and fast acceleration stimuli. Other than this physiological difference, we assume that the shrunken cupula causes different SC activity to stimuli with different acceleration. In this study, we examined the physiological activity of SC with half-sized cupula in response to slow and fast stimuli.

Material and methods

Fifteen bullfrogs (Rana catesbeiana) were used. The posterior semicircular canal (PSC) was isolated in frog Ringer's solution. The utricular side of the ampullary wall was cut and the cupula was stained with India ink. The cupula was then removed with fine glass pipettes. The technique for removing the cupula was reported in detail previously [5]. All experiments were conducted according to the rules of the animal experiment ethical committee of Tokyo Medical University. The following two experiments were performed.

Experiment 1: replacement of the entire cupula

The cupula was first removed and then entirely replaced on the crista (Figure 1). The PSC ampullary nerve was sucked into the glass suction electrode to record the compound action potentials (CAP). A fine polyethylene tube was inserted into the cut end of the canal. Mechanical endolymphatic flow was delivered

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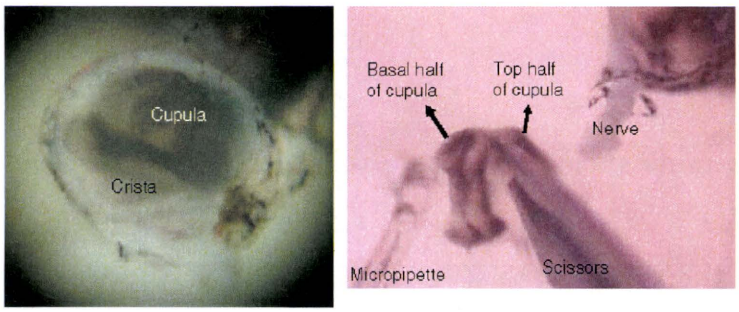

Figure 1. A photograph of the replaced entire cupula and cupula sectioning. The cupula was stained with India ink. The replaced cupula fills the entire space of the ampulla (left). The cupula was just sectioned with scissors and was separated into two parts, basal and top (right). The micropipette was used to place the cupula between the scissor blades.

through this tube by manually driving a micromanipulator. The volume of the endolymphatic flow as a stimulus was 0.012 µl. Fast and slow stimuli were created by setting short and long rise-fall times. The short rise-fall time was set to be 1 s and the long one was 5 s. The whole duration of the stimulus was 10 s. The stimuli with short and long rise-fall time were designated Stim-1 and Stim-5, respectively.

Experiment 2: sectioning of the cupula and replacement of the half cupula

The removed cupula was sectioned in half in the plane parallel to the cupular surface facing the sensory epithelia, which was designated as the cupular base. This was termed as horizontal sectioning, as reported previously [6]. Fine scissors were used to section the cupula. A fine glass micropipette was used to gently move and settle the cupula between the blades of the scissors (Figure 1). The cupula has a thinner central portion and thicker side portions, creating a cut surface with a dumb-bell shape [6]. Therefore, horizontal sectioning was relatively difficult, requiring considerable skills and practice, as compared with vertical sectioning. All procedures were performed under a dissection microscope. A basal half of the cupula was replaced on the crista so that the base sat snugly on the whole crista.

After replacing the cupula, the PSC CAP was recorded in the same way as in experiment 1. The same stimuli, Stim-1 and Stim-5, were used.

The CAPs recorded in experiments 1 and 2 were converted into spike density histograms and were analyzed in terms of the maximum spike counts and duration of the response. The maximum spike counts of Stim-5 were expressed as percentages with those of the Stim-1 as 100%. The duration of Stim-5 was also expressed as percentages with that of Stim-1 as 100%.

Results

The entire cupula could be removed using the glass micropipette without disturbing or altering its structure. It was snugly replaced on the crista filling the entire ampullary wall as in the condition before cupula removal (Figure 1).

Experiment 1: PSC CAP in response to Stim-1 and Stim-5 after the entire cupula replacement

The maximum spike count percent values of Stim-5 were around 110% (Figure 2, left column of the left graph), giving an average of 109.7 ± 17.5. The duration percent values of Stim-5 were around 110% (Figure 2, left column of the right graph), giving an average of 111.7 ± 11.7.

Experiment 2: sectioning of the cupula and replacement of the half cupula

The cupula could be horizontally sectioned into half using fine scissors (Figure 1). The cupula has a relatively solid framework and was not fragmented or distorted by the sectioning procedure. The basal half of the cupula was replaced on the crista showing open space between the cupula top and the ampullary roof (Figure 3).

PSC CAP in response to Stim-1 and Stim-5 after the half cupula replacement was recorded. Examples of spike density histograms due to Stim-1 (left) and Stim-5 (right) are shown in Figure 4. The maximum spike counts were smaller in Stim-5 than in Stim-1 in all preparations (Figure 2, right column of the left graph), giving an average percent value of Stim-5, 79.8 ± 12.1%. The duration of CAP was greater in Stim-5 than in Stim-1 except for one preparation (Figure 2, right column of the right graph), giving an average percent value of Stim-5, 163.1 ± 68.7%.

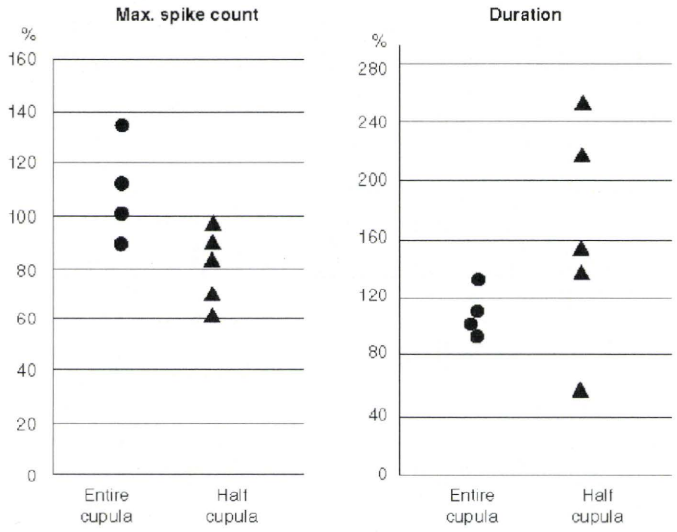

Figure 2. The CAP maximum spike counts (left graph) and the duration (right graph) of Stim-5 expressed as percentages with those of Stim-1 as 100% in the entire (left column) and half cupula (right column) replacement. In the entire cupula replacement, the percentage values of the maximum spike counts were scattered around 110%, giving an average of 109.7%. In the half cupula replacement, they were always smaller than 100%, giving an average of 79.8%, indicating that the CAP becomes smaller with half cupula under slow stimulus. In the entire cupula replacement, the percentage values of the CAP duration were scattered around 110%, giving an average of 111.7%. In the half cupula replacement, they were >100% except for one case, giving an average of 163.1%, indicating that the CAP becomes short with the half cupula under fast stimulus.

Discussion

The cupula plays an important role as a mechano-transducer of the SC receptor. However, the past studies have mainly focused on sensory cells and neurons and not on the appendix part, such as the cupula. The appendix part of the cochlea is the tectorial membrane and studies have revealed its disorders as a possible cause of hearing loss [7,8]. On the other hand, studies on the cupula are very scarce, possibly because of its morphological vulnerability. In the previous experiment using gentamicin we found that the cupula shrinks from the margin, leaving the basal part that faces the sensory epithelia intact [1]. Even when the cupula shrinks, the sensory epithelia can remain intact [1]. Shrinkage of the cupula creates space between the cupula top and the ampullary roof. This space allows the endolymph to escape when the stimulus is slow, resulting in less pressure effect on the cupula and eventually the smaller CAP spikes, as shown in experiment 2. However, the CAP duration is longer in slow stimulus and shorter in fast stimulus. Short duration in the fast stimulus is possibly due to quick swing back of the half cupula without the anchoring effect of its margin with the ampullary wall. These findings are in good contrast with experiment 1, which showed CAP with similar spike counts and duration between Stim-1 and Stim-5. The smaller CAP magnitude with the half cupula in slow stimulus may further lead to reduced caloric response. We assume that the shrunken cupula evokes different SC activity to vestibular tests with slow and fast acceleration stimuli.

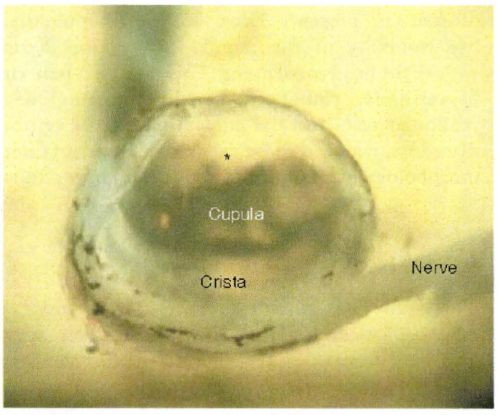

Figure 3. A photograph of the replaced half cupula. The space between the cupula and the ampullary wall is shown (asterisk).

The head shaking test (HST) has been used to examine unilateral vestibular asymmetry in response

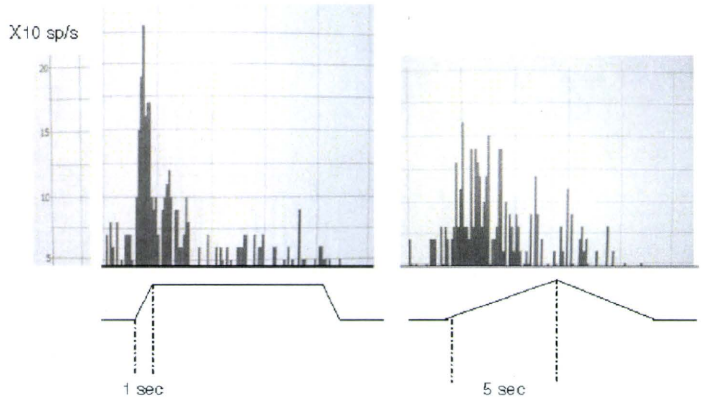

Figure 4. Examples of spike density histograms of PSC ampullary CAP due to fast Stim-1 (left) and slow Stim-5 (right) stimuli. The fast stimulus (1 s onset, Stim-1) induced greater potential with shorter duration (left) and the slow stimulus (5 s onset, Stim-5) induced smaller and longer CAP (right). The lower diagram shows the configuration of the fast and slow stimuli.

to quick alternating head acceleration [2–4]. Head shaking nystagmus (HSN) is induced by asymmetric activity between bilateral horizontal SC. During head shaking, SC asymmetry builds up, leading to accumulation of the velocity storage mechanism [9]. With sudden cessation of head shaking, the stored SC activity discharges nystagmus through the VOR pathway [2]. The correlation between positivity of HSN and caloric canal paresis (CP) has been studied. Some studies reported discrepancy of the results between the caloric test and HST in vestibular disorders. In Meniere's disease the proportion of caloric CP is greater than the proportion of positive HSN [10]. Wei et al. reported that HSN was recorded in only 40% of subjects with caloric CP in the vestibular lesions [4]. Jacobson et al. [9] showed 21% positive HSN and 44% positive caloric CP in unilateral vestibular disorder. This discrepancy had been thought to be due to the different physiological activity of SC responding to the stimuli with different frequencies [9,10]. For the caloric test, the valid frequency is about 0.003 Hz, while for the HSN test it is 2 Hz [9,11]. In the caloric test, the cells sensitive to lower frequency stimuli are mainly activated and in HST the cells sensitive to higher frequency are activated.

Other than this physiological difference, change of the cupula morphology potentially plays a significant role in HSN. In the present study, PSC CAP markedly reduced when the stimulus was slow. From this finding, we assume that when the cupula shrinks, the PSC activity to slower stimuli including caloric stimulus is reduced, while the activity to faster stimuli is maintained. This maintained response to fast stimuli possibly results in less asymmetry of bilateral SC function, leading to less emergence of HSN. Consequently, some patients with caloric CP may show very slight HSN. It is known that in Meniere's disease endolymphatic hydrops induces distention of the membranous labyrinth [12,13]. If the ampullary membrane distends, it creates space around the cupula. This space exerts a similar effect to the shrunken cupula and may also contribute to reduced caloric response. Therefore, in Meniere's disease, cupula shrinkage as well as distention of the membranous labyrinth can develop, and hence the chance of reduced caloric response may increase even more than for other vestibular lesions.

The space between the cupula top and the ampullary roof also changes the sensitivity of the SC. The shrunken cupula potentially behaves as a floppy cupula with a mobile top part, thus resulting in more intense nystagmus, particularly when cupulolithiasis is present. Even without cupulolithiasis hypermobility of the cupula may cause dizziness with slight head movement. This may be a new entity of vestibular pathology. For interpretation of the vestibular tests and the clinical picture of vestibular disorders, we need to be aware of changes of cupular morphology in addition to hair cell or neuron lesions.

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半規管瘻孔症例の臨床的検討

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Clinical observation of a semicircular canal fistula associated with cholesteatoma

Eriko SHINADA, Mamoru SUZUKI, Sachie KAWAGUCHI, Nobuhiro NISHIYAMA, Akira HAGIWARA, Yasuo OGAWA and Atsushi KAWANO

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半規管瘻孔は真珠腫性中耳炎の合併症の一つであり、手術症例の約10%に認められると報告されている。内耳の開放は術後の骨導閾値を上昇させることがあると考えられていたが、病変の郭清によって術後に骨導閾値が低下したという報告もある。今回われわれは真珠腫性中耳炎で半規管瘻孔がみられた症例について検討した。対象は1997年から2009年までの12年間に東京医科大学病院耳鼻咽喉科で手術を施行した真珠腫性中耳炎症例のうち半規管瘻孔が観察された19例19耳である。初診時の主訴はめまいが最も多く、約半数を占めていた。ついで難聴、耳閉が32%、耳漏が21%であった。瘻孔症状があったのは37%であった。瘻孔の大きさは2mm以下を小瘻孔、それより大きいものを大瘻孔に分けると、大多数が大瘻孔であった。瘻孔の場所は大半が外側半規管であったが、後半規管の瘻孔が1耳あった。術前の気導聴力は3分法平均で72.5dB、骨導は3分法平均で37.4dBであった。瘻孔の大きさと聴力には関連はなかった。術後に骨導聴力が10dB以上改善した症例は3耳あり、うち1耳は15dB以上の改善であった。骨導が著明に悪化した症例はなかった。また、術後全例でめまいは改善した。

Key words：semicircular canal fistula、cholesteatoma、vertigo、tympanoplasty

はじめに

半規管瘻孔は真珠腫性中耳炎の合併症の一つであり、手術症例の約10%に認められると報告されている[1),2)]。内耳の開放は術後の骨導閾値を上昇させることがあると考えられていたが、病変の郭清によって術後に骨導閾値が低下したという報告もある[3)]。瘻孔の対処法は聴覚、前庭機能、真珠腫の完全除去などの要素を総合的に考慮した上で決定する必要があり、瘻孔の病態や臨床像を把握しておくことは重要である。今回われわれは真珠腫性中耳炎にみられた半規管瘻孔症例について検討したので報告する。

対象と方法

1997年10月から2009年9月までの12年間に東京医科大学病院耳鼻咽喉科で手術を施行し、術後当院外来で経過観察した真珠腫性中耳炎症例のうち、半規管瘻孔があった19例19耳を対象とした。男性14例、女性5例であり、年齢は11歳から80歳（平均55.7歳）であった。聴力評価は3分法で行い、術直前1カ月以内および術後6カ月以降で最終検査時の値を用いた。聴力データの不十分な症例は除外した。段階手術例においては二期的手術後6カ月以降のものを用いた。瘻孔の大きさはGacekら[4)]や斎藤ら[5)]の分類を参考に、2mm以下を小、それより大きいものを大とした。

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