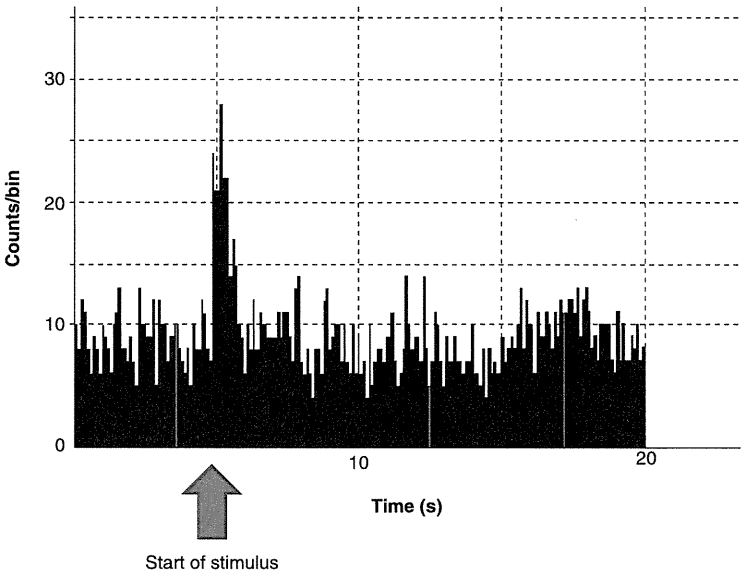

Figure 2. Spike density histogram of ampullary nerve compound action potential (CAP). Note the short duration of the response.

Morphological changes of the cupula

Various changes of the cupula were observed, including shrinkage, deformity, and volume enlargement, which are somewhat different from the changes that have been reportedly observed due to GM intoxication. Mild change (grade I) was represented by shrinkage from the margin, which is identical to that due to GM intoxication (Figure 4). Grade I and II changes of the cupula were observed in 46 SCs (57.5%) and 4 SCs (5.0%), respectively, in a total of 80 SCs. Grade I and II changes were observed in 62.5% of a total number of 80 SCs (Table I). Grade III and IV changes were observed in 7 SCs (8.8%) and 18 SCs (22.5%), respectively. Grade III and IV changes were observed in 31.3% of a total of

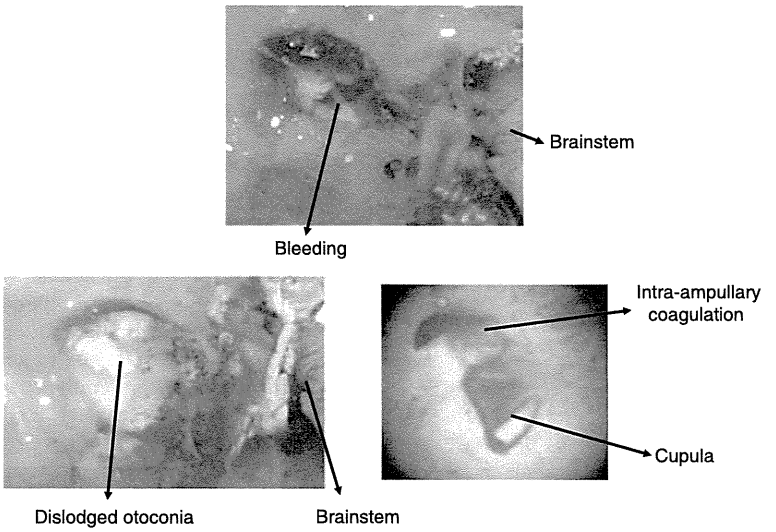

Figure 3. Findings of the inner ear at the site of puncture show bleeding in the labyrinth (top), dislodged saccular otoconia (left, below), and coagulated mass attached to the cupula (right, below).

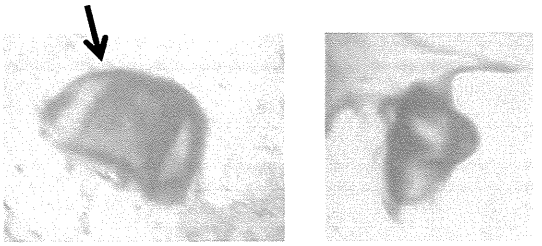

Figure 4. Changes in the anterior semicircular canal cupula: grade I change (left) and grade II change (right). The arrow indicates a slight indentation in the cupular margin.

80 SCs. Other noteworthy findings included marked deformity and enlarged volume of the cupula. Figure 5 shows examples of the enlarged and elongated cupulae observed in the LC. Occasionally, the cupula transformed into soft and amorphous structures (Figure 5). These aberrantly shaped cupulae were observed in 5 of the 80 SCs (6.3%).

Cupular changes were evaluated separately in the short-term and long-term groups. Grade I–II changes were observed in 24 of 32 SCs (75.0%) in the short-term group and in 26 of 48 SCs (54.2%) in the long-term group. Grade III–IV changes were observed in 7 of 32 SCs (21.9%) in the short-term group and in 18 of 48 SCs (37.5%) in the long-term group (Table I). In the long-term group, the cupular changes tended to be severe. A cupula with aberrant morphology was observed in 1 of 32 SCs (3.1%) in the short-term group and in 4 of 48 SCs (8.3%) in the long-term group (Table I).

CAP results

The average maximum spike counts of 8 normal PCs after removal of the cupula were 209.6 ± 24.8 spikes/s.

Table I. Degrees of cupular change in the short-term and long-term groups.

	Short-term group		Long-term group		Total	
Grade	*n*	%	*n*	%	*n*	%
I	21	65.6	25	52.1	46	57.5
II	3	9.4	1	2.1	4	5.0
III	2	6.3	5	10.4	7	8.8
IV	5	15.6	13	27.1	18	22.5
Aberrant shape	1	3.1	4	8.3	5	6.3
Total	32		48		80	

CAP was measured in 28 SCs in the long-term group. Among 28 SCs, the measurement site was the LC in 10, AC in 9, and PC in 9. A CAP with a maximum spike count of more than 100 spikes/s was recorded in 20 of 28 SCs (71.4%) in this group. The average maximum spike counts ranged from 100.4 spikes/s to 250.2 spikes/s, with an average of 188.3 ± 44.1 spikes/s, which was not significantly different from that of the normal PC. As shown in Figure 2, the duration of CAP in the SCs without a cupula was extremely short, compared with that of CAP in the normal SCs with a cupula [4], because the sensory cilia that are deviated by the endolymphatic flow quickly swing back without being held by the cupula.

The morphological changes in the cupula were compared with the CAP results. CAP was obtained in 14 of 16 SCs (87.5%) in those showing grade I change. CAP was obtained in 5 of 10 SCs (50.0%) in those showing grades III–IV change (Table II). The overall CAP positivity rate was 71.4%. This indicates that the physiological activity of the sensory epithelia can be maintained, even when the cupula is severely damaged.

Discussion

Most benign paroxysmal positional vertigo (BPPV) cases have a good prognosis, but some cases are still refractory. SC plugging is considered to be effective for the control of refractory BPPV [7]. However, in a case previously reported by one of the authors, plugging was not effective. A morphological change in the SC, particularly in the cupula, was suspected to be the cause. This prompted our studies of the cupula morphology. In the most recent experiment, the cupula shrank from either the top part or the margin after GM injection into the perilymphatic space [6]. Cupula shrinkage left a space between the cupula margin and the ampullary wall, thus hypermobilizing the cupula. We assume that this is the cause of the ineffectiveness of the previously reported plugging surgery.

In the present study, the membranous labyrinth was ruptured by inserting the needle, with the assumption that several pathological conditions such as the mixing of perilymph and endolymph or labyrinthitis may develop. We were interested in what kind of changes the cupula and sensory epithelia might undergo, and in whether or not the physiological activity of the sensory epithelia changes is important, since it directly affects the development of vertigo and the caloric response.

Grade III or more change in the cupula was detected in 31.3% of the total number of SCs. We suspected that the cupula damage occurred from the

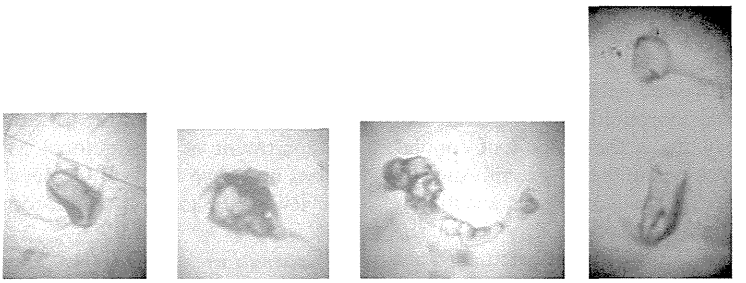

Figure 5. Changes in the lateral semicircular canal cupula. Amorphous, elongated, and separation changes were observed.

mixing of perilymph and endolymph, or the inflammatory changes in the inner ear. The reduction in cupula size started from either the top part or the margin of the cupula, which is similar to the reduction seen in cases of GM intoxication. The supporting cells of the ampulla and parts of the sensory cells are known to contribute to the metabolism of the cupula [8,9]. This may be the reason why the margin of the cupula is the first to shrink, with shrinkage of the bottom part occurring later, as it is close to the site of the metabolism. Otogelin (otog) is one of the main proteins that form the cupula and that anchor the cupula base to the crista [1,2]. In the absence of the otog gene, the cupula is known to be detached from the crista [10]. In acquired pathology, the top part of the cupula is the first to decay, as shown in our previous studies. Grade III–IV changes in the cupula were observed in 21.9% of those in the short-term group and 37.5% of those in the long-term group. The changes in the cupula tended to be more severe in the long-term group. This is possibly because the chemical and inflammatory changes of the endolymph had accumulated over a long period and had directly affected the cupular structure.

We studied the physiological function of the SC after puncturing the membranous labyrinth by recording the CAP. Against our expectations, CAP measurement was obtained in 71.4% of the examined SCs. Furthermore, the CAP could be obtained in half of the SCs with grade III or more cupular change. The changes in the cupula had occurred to a similar degree to those in the cupula due to GM injection, but a greater portion of sensory epithelia remained functionally viable than in cases given a GM injection.

Table II. CAP positivity in the long-term group.

Grade	Total (*n*)	CAP –	CAP +	CAP positive rate
I	16	2	14	87.5%
II	0	0	0	0.0%
III	3	2	1	33.3%
IV	7	3	4	57.1%
Aberrant shape	2	1	1	50.0%
Total	28	8	20	71.4%

In the animals that received GM injection, damage to the sensory epithelia appeared earlier than the cupular change. For example, 3 days after GM injection, three of seven SCs with grade I cupular change already showed severe damage to the sensory epithelia [6]. In this labyrinthine puncture model, the cupular change tended to appear earlier than the damage to the sensory epithelia. While GM directly affects the sensory epithelia, the labyrinthine puncture induces milder changes of the sensory epithelia due to either a secondary effect of environmental change or inflammation within the inner ear. However, the cupula is more sensitive to this insult, because it exists within the endolymph.

The normal cupula works as a separating wall in the ampullary space. The cupula deviates according to the endolymphatic flow caused by head rotation. This movement is disturbed when the cupula shrinks, as was seen in the GM injection. Reduction of the cupula size induces escape of the endolymphatic flow, thus leading to reduction of the vestibulo-ocular reflex and caloric response. Furthermore, in cupulolithiasis, more severe symptoms and nystagmus may develop due to an increase in cupula mobility, especially when the sensory epithelia are sufficiently functioning, as was indicated by a positive CAP in the present series.

An aberrant morphology of the cupula such as an enlarged or elongated volume was observed in 3.1% of models in the short-term group and 8.3% of those in the long-term group, but was not observed in those

of GM intoxication [6]. Occasionally, the large or elongated volume of the cupula filled the ampullary space or the canal lumen. This condition may also disturb effective sensory cell activation. The mechanism of this abnormal morphology is not clear, but one possibility is that this is the process of cupular regeneration that developed in the long term. Another mechanism could be the attachment and accumulation of the protein or degenerative product in the cupula, but this remains to be investigated. From a clinical point of view, all of the above pathologies may occur when the labyrinth sustains a mechanical injury after surgery or head trauma. The human labyrinth is particularly susceptible to mechanical damage because of its thin and vulnerable membranous labyrinth.

It has been suggested that the difference in the changes between the cupula and the sensory epithelia depends on the type and site of damage within the inner ear, and that this difference modifies the clinical features of vestibular disorders. Future studies should include the molecular biology of the mechanism of cupular damage and its regeneration process. The optimal method for accelerating cupular regeneration may become an important tool to cure vertigo with cupular damage.

Conclusions

The labyrinthine injury model created by puncturing the membranous labyrinth induced various kinds of cupular changes, including shrinkage. Cupular change was more severe after a longer survival period, and a large or elongated volume of the cupula was also seen. In this model, CAP of the ampullary nerve could be recorded even when the cupular change was severe. Cupular change after disruption of the membranous labyrinth may be a pathology of vestibular disorders.

Acknowledgments

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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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MAIN ARTICLE

Efficacy of physical therapy for intractable cupulolithiasis in an experimental model

K OTSUKA, M SUZUKI, M NEGISHI, S SHIMIZU, T INAGAKI, U KONOMI, T KONDO, Y OGAWA

Department of Otolaryngology, Tokyo Medical University, Japan

Abstract

Objective: To investigate what kinds of stimuli are effective in detaching otoconia from the cupula in three experimental models of cupulolithiasis.

Methods: Three experimental models of cupulolithiasis were prepared using bullfrog labyrinths. Three kinds of stimuli were applied to the experimental models. In experiment one (gravity), the labyrinth preparation was placed so that the cupula-to-crista axis was in the horizontal plane with the canal side in the downward position. In experiment two (sinusoidal oscillation), the labyrinth preparation was placed 3 cm from the rotational centre of a turntable, which was sinusoidally rotated with a rotational cycle of 1 Hz and a rotational angle of 30°. In experiment three (vibration), mechanical vibration was applied to the surface of the bony capsule around the labyrinth using a surgical drill.

Results: In experiments one, two and three, the otoconial mass was respectively detached in 2 out of 10 labyrinth preparations, none of the labyrinth preparations, and all of the labyrinth preparations.

Conclusion: Vibration was the most effective stimulus for detaching the otoconia from the cupula in these experimental models of cupulolithiasis.

Key words: Benign Paroxysmal Positional Vertigo; Pathology; In Vitro; Bullfrog; Otoconia

Introduction

The cupula consists mainly of mucopolysaccharide and is very adhesive in nature. This adhesiveness facilitates easy attachment of the otoconia, resulting in cupulolithiasis. Schuknecht[1] reported cupulolithiasis in which the otoconia attach to the cupula, making it gravity-sensitive. In our experience, cases of intractable cupulolithiasis need careful treatment. Therefore, physical therapy with maximal efficacy should be developed.

This study aimed to investigate what kinds of stimuli are effective in detaching the otoconial mass from the cupula in experimental models of cupulolithiasis.

Materials and methods

The experimental models of cupulolithiasis were prepared using bullfrogs (*Rana catesbeiana*) weighing 110–220 g. After induction of deep anaesthesia with ether, the bullfrogs were decapitated and the bony labyrinth was removed and placed in Ringer solution according to the method of Suzuki *et al.*[2] The caudal otic capsule was chiselled so that the entire posterior semicircular canal was exposed. The remaining membranous labyrinth was left encapsulated in the bony capsule. The membranous labyrinth was carefully cut at the crus commune to create a tiny, 0.5 mm opening. A small piece of otoconia, removed from the sacculus of the other ear, was introduced through this opening into the canal lumen. The position of the labyrinth preparation was adjusted so that the otoconial mass was fixed onto the cupula.

Three different kinds of stimulus were then used in this experimental model of cupulolithiasis, in order to determine the most effective stimulus for detaching the otoconial mass: gravity, sinusoidal oscillation and vibration.

A dissection microscope (SZX12; Olympus, Tokyo, Japan) was used for observation of the otoconial mass.

All experiments were conducted according to the ethical rules for animal experiments at Tokyo Medical University.

Experiment one: gravity

The first experiment tested the effect of gravity, using 10 membranous labyrinth preparations. The labyrinth preparation was placed in a glass dish filled with

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Ringer solution (100 ml) so that the cupula-to-crista axis was in the horizontal plane with the canal side in the downward position. The labyrinth preparation was maintained in this position for 30 minutes. The otoconial mass attached to the cupula was checked every 10 minutes (Figure 1).

Experiment two: sinusoidal oscillation

The second experimental model assessed the effect of sinusoidal oscillation, using 10 membranous labyrinth preparations. The labyrinth preparation was placed in a glass dish filled with Ringer solution (100 ml), which was magnetically fixed to a turntable (FRA-02; First, Tokyo, Japan). The labyrinth preparation was placed 3 cm from the rotational centre. The cupula-to-crista axis was placed along a line pointing towards the rotational centre. The turntable was sinusoidally rotated with a rotational cycle of 1 Hz and a rotational angle of 30°. The sinusoidal rotation was maintained for 30 minutes. The otoconial mass attached to the cupula was checked every 10 minutes (Figure 2).

Experiment three: vibration

The third experimental model tested the effect of vibration, using 14 membranous labyrinth preparations. The labyrinth preparation was placed in a glass dish (100 ml) in the same position as in experiment one. Mechanical vibration was applied to the top surface of the bony otic capsule of the labyrinth preparation using a surgical drill (BL-F5A; Osada Electric, Tokyo, Japan). A cutting burr with a 5 mm tip diameter was used. The frequency of the vibration, as measured by a vibration analyser (VA-12; Rion, Tokyo, Japan), was 340 Hz. The otoconial mass attached to the cupula was checked during the procedure. Care was taken not to rupture the membranous labyrinth (Figure 3).

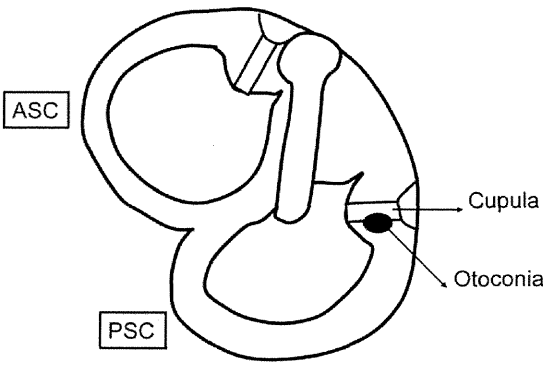

FIG. 1

Diagram representing experiment one (gravity). The labyrinth preparation was placed so that the cupula-to-crista axis was in the horizontal plane with the canal side in the downward position. The otoconial mass was checked every 10 minutes for 30 minutes. ASC = anterior semicircular canal; PSC = posterior semicircular canal.

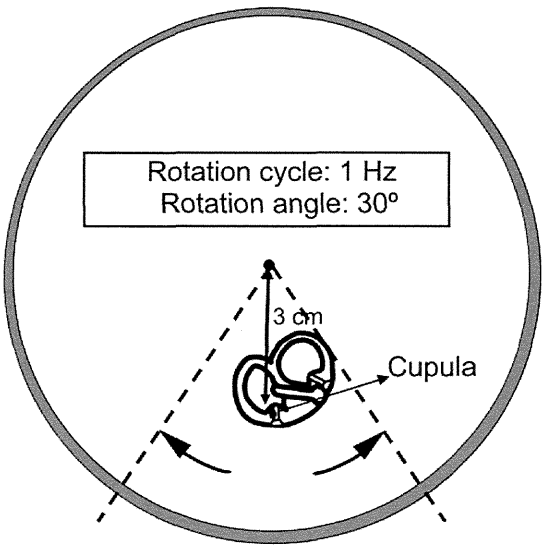

FIG. 2

Diagram representing experiment two (sinusoidal oscillation). The labyrinth preparation was placed 3 cm from the centre of a turntable. The cupula-to-crista axis was placed along a line pointing towards the centre. Oscillation was applied for 30 minutes. The turntable was rotated with a rotational cycle of 1 Hz and a rotational angle of 30°. The otoconial mass was checked every 10 minutes.

Results

Experiment one: gravity

The otoconial mass was detached within 30 minutes in 2 of the 10 labyrinth preparations used in experiment one; in these cases, the detachment times were 10 and 30 minutes.

Experiment two: sinusoidal oscillation

The otoconial mass was not detached from the cupula within 30 minutes in any of the labyrinth preparations in experiment two.

Experiment three: vibration

The otoconial mass was detached from the cupula in all labyrinth preparations in experiment three (Figure 4). The detachment times ranged from 10 seconds to 5 minutes 10 seconds. The mean detachment time was 2 minutes 20 seconds.

Discussion

Benign paroxysmal positional vertigo (BPPV) is mainly caused by movement of detached otoconia within the semicircular canal (canalolithiasis), or by movement of otoconia attached to the cupula (cupulolithiasis). In our group's previous experiments,[3,4] both cupulolithiasis and canalolithiasis effectively stimulated the cupula and were thus potentially valid mechanisms of BPPV. The clinical features of typical BPPV are characterised by brisk, rotatory, dominant nystagmus with a latency of several seconds and a short duration. This feature could be explained more favourably

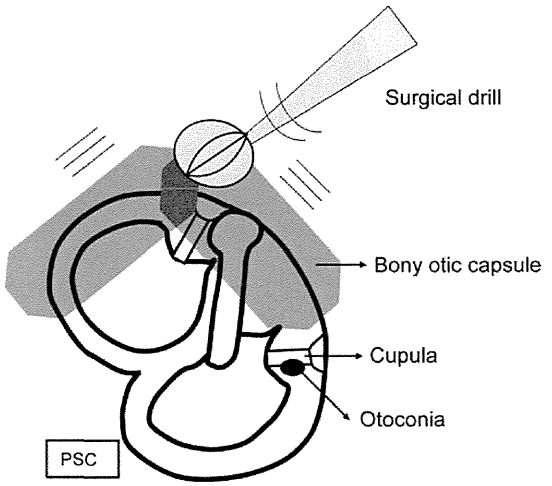

FIG. 3

Diagram representing experiment three (vibration). Mechanical vibration at 340 Hz was applied to the bony capsule near the labyrinth using a surgical drill. The otoconial mass was checked during the procedure.

by the mechanism of canalolithiasis. However, there is another type of positional vertigo with negligible latency and a long duration of more than several minutes. This type of vertigo could be explained by cupulolithiasis. Based on our experience, cases of intractable cupulolithiasis occur and can even require canal plugging surgery.[5] Therefore, the development of physical therapy with maximal efficacy for cupulolithiasis is highly desirable.

Chiou *et al.*[6] have reported the use of a forced prolonged position, wherein patients with cupulolithiasis were required to lie on the side of weaker nystagmus for 12 hours. Symptoms were relieved in all patients after four sessions. However, in our experimental study the otoconial mass was detached in only 2 out of 10 labyrinth preparations following 30 minutes' exposure to gravity. With longer exposure times, it is possible that more otoconia could be detached. The forced prolonged position technique is effective but requires patients to remain in a lying position for a long period, which is uncomfortable for some.

White *et al.*[7] used several types of rolling or brisk deceleration manoeuvres (developed by Lempert and Tiel-Wilck,[8] Gufoni *et al.*,[9] Asprella Libonati *et al.*,[10] and Brandt and Steddin)[11] as well as head-shaking. The Gufoni manoeuvre first places patients in the sitting position, then makes them quickly lie down towards the affected side, and finally makes them rotate their head 45° downward and maintain this position for 2 to 3 minutes.[9] The Vannucchi–Asprella manoeuvre rapidly moves patients from the sitting to the supine position, then turns the head rapidly to the unaffected side, then returns the patient to the sitting position, and finally returns the head to the midline. This manoeuvre is repeated five to eight times.[10] After these manoeuvres, White *et al.*[7] found that the symptoms of all canalolithiasis patients were resolved, but the symptoms of only 50 per cent of cupulolithiasis patients were resolved.

In our experimental study, none of the otoconial masses were detached by sinusoidal oscillation in any of the labyrinth preparations. This result is compatible with the low efficacies noted when the above-mentioned manoeuvres were applied to patients with cupulolithiasis.

Kim *et al.*[12] have reported a new cupulolith repositioning manoeuvre. Beginning with the patient in the supine position, the patient's head is turned 135° toward the affected side. Mastoid oscillation is then applied to the affected side, using a 60-Hz, hand-held vibrator, for 30 seconds. The otoconia at the canal side of the cupula will be detached by this manoeuvre. The patient's head is returned to the supine position. Next, the patient's head is turned 90° towards the unaffected side and mastoid oscillation is repeated once. The otoconia at the utricular side of the cupula will be detached by this manoeuvre. Finally, the patient's head is rotated 90° in the prone position and the patient is slowly brought to a sitting position. Using this manoeuvre, symptoms were resolved in 62 per cent of patients in one session, and in 97 per cent of patients after six sessions.

Our experimental study found that the otoconial mass was detached by mechanical vibration in all labyrinth preparations. This result is compatible with the high efficacy rate of Kim and colleagues' cupulolith repositioning manoeuvre.

- **Cupulolithiasis is intractable because of otoconial adhesion to the cupula**
- **This experimental study tested the effectiveness of various stimuli in resolving cupulolithiasis**
- **The effect of gravity, sinusoidal oscillation and mechanical vibration was tested**
- **Vibration was most effective in detaching an otoconial mass from the cupula**

However, the question remains whether vibration could also dislodge the utricular otoconia. Amir *et al.*[13] reported a case of BPPV which occurred after the use of a whole-body vibration training plate. Similarly, our previous experiments, using bullfrog membranous labyrinth preparations, indicated that otoconia were dislodged from the utricle and moved into the posterior semicircular canal in half of the preparations after 15 minutes of vibration using a surgical drill.[4] It takes longer for vibration to dislodge the otoconia from the utricle than from the cupula. Fine morphological studies show that the utricular otoconia are connected to each other with fine fibrils and are embedded in a gelatinous substance made of mucopolysaccharide.[14,15] The whole otoconial mass is covered by a

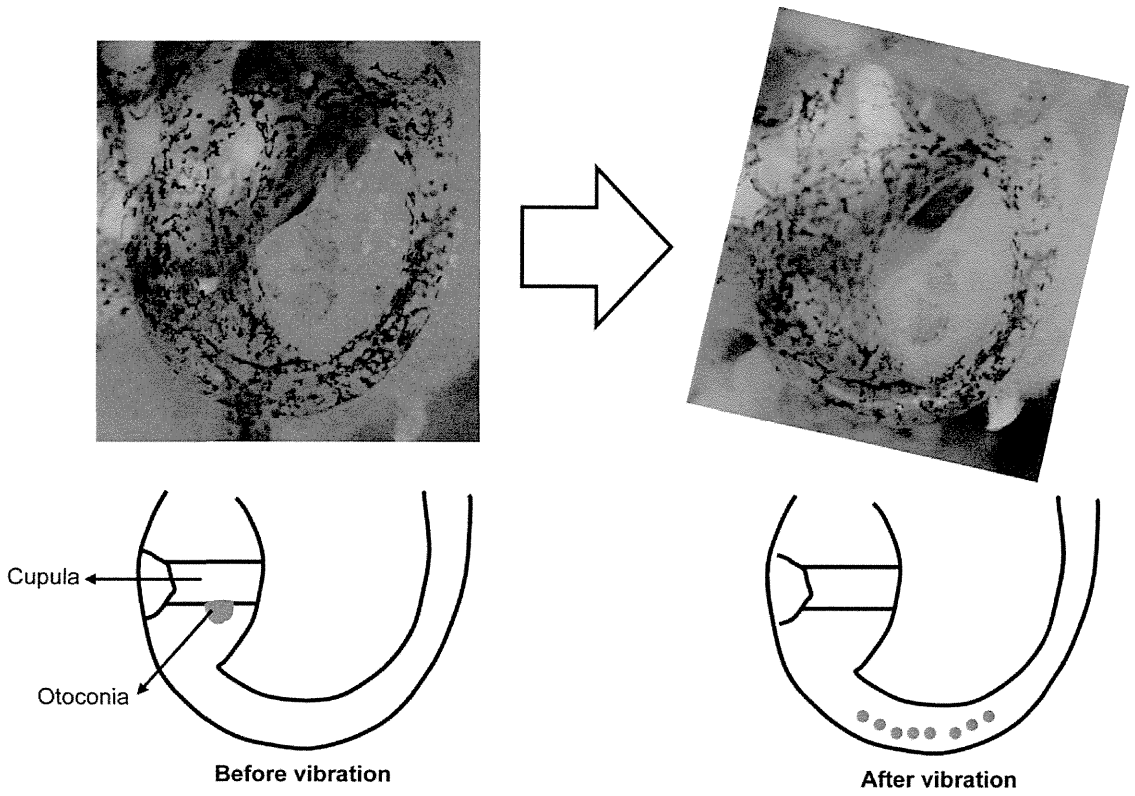

FIG. 4

Magnified photographs and diagrams for experiment three (vibration). Before vibration, the otoconial mass was attached to the cupula. After vibration, the otoconial mass was detached from the cupula and was separated into pieces.

supraotoconial layer.[16] This may be one reason why short-duration vibration can dislodge the otoconia from the cupula without dislodging the utricular otoconia.

Conclusion

In this experimental study of cupulolithiasis in a bull-frog membranous labyrinth model, over 30 minutes, the otoconial mass was detached by gravity in only 2 of 10 labyrinth preparations, and was not detached by sinusoidal oscillation in any preparation. However, the otoconial mass was detached by mechanical vibration in all labyrinth preparations, over the same time period; the mean detachment time was 2 minutes 20 seconds. Thus, mechanical vibration was the most effective stimulus for detaching the otoconia from the cupula in this experimental model.

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Address for correspondence:
Dr Koji Otsuka,
Department of Otolaryngology,
Tokyo Medical University,
6-7-1 Nishi-shinjuku,
Shinjuku-ku,
Tokyo 160-0023, Japan

Fax: +81 (0)3 3346 9275
E-mail: otsukaent@aol.com

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MAIN ARTICLE

Relationship between clinical features and therapeutic approach for benign paroxysmal positional vertigo outcomes

K OTSUKA, Y OGAWA, T INAGAKI, S SHIMIZU, U KONOMI, T KONDO, M SUZUKI

Department of Otolaryngology, Tokyo Medical University, Japan

Abstract

Objective: To examine the clinical features, age and gender distribution of patients, treatment methods, and outcomes of benign paroxysmal positional vertigo.

Methods: This paper reports a review of 357 patients treated for this condition at a single institution over a duration of 5 years. Patients with posterior canal benign paroxysmal positional vertigo were divided into two groups: one group underwent the Epley manoeuvre and the other received medication. The lateral canal canalolithiasis patients were also divided into two groups: one underwent the Lempert manoeuvre and the other received medication. Lastly, the lateral canal cupulolithiasis patients were treated with medication and non-specific physical techniques.

Results and conclusion: For patients with posterior canal benign paroxysmal positional vertigo, resolution time was significantly shorter in the Epley manoeuvre group than in the medication group. For the lateral canal canalolithiasis patients, resolution time was significantly shorter in the Lempert manoeuvre group than in the medication group. Resolution time was significantly longer in the lateral canal cupulolithiasis patients than in the other patients. The average age of patients increased with the number of recurrences, as did predominance in females. Average age and rate of sensorineural hearing loss were significantly higher in patients with intractable benign paroxysmal positional vertigo compared with those in the curable benign paroxysmal positional vertigo group.

Key words: BPPV; Benign Paroxysmal Positional Vertigo; Vertigo, Peripheral; Therapy; Diagnosis; Recurrence; Prognosis

Introduction

Benign paroxysmal positional vertigo (BPPV) is a common vestibular disorder. It is classified into two major types according to the nature of the induced nystagmus. The most common type is posterior canal canalolithiasis. The induced nystagmus is typically of a rotatory, vertical nature, with up beating when the head is hanging down, and down beating when in the sitting position. Nystagmus induced by posterior canal canalolithiasis is characterised by its short duration and latency.

Benign paroxysmal positional vertigo that presents with a direction-changing horizontal nystagmus, mainly induced in the right and left side head-down positions, is called lateral canal BPPV. Lateral canal BPPV is further classified into two types according to the direction of the induced nystagmus, namely geotropic nystagmus and apogeotropic nystagmus. The underlying mechanism of geotropic nystagmus is thought to be canalolithiasis of the lateral canal, and that of apogeotropic nystagmus is considered to be cupulolithiasis of the lateral canal.

This study aimed to examine the age and gender distribution of patients, clinical types of BPPV, therapeutic methods, and outcomes of BPPV. We focused on recurrent and intractable BPPV with regard to prognosis and outcomes.

Materials and methods

Of 3797 vertigo patients treated at our department from August 2004 to July 2009, we reviewed 357 BPPV patients (9.4 per cent). All patients with dizziness or vertigo were tested using the Dix–Hallpike manoeuvre. Assessment of lateral head rotation in the supine position was then made. Nystagmus was observed using an infrared charge-coupled device camera.

Posterior canal BPPV was diagnosed on the basis of the following criteria: (1) a history of brief episodes of

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positional vertigo, (2) the absence of an identifiable central lesion that might explain the positional vertigo, and (3) a direction-changing torsional nystagmus triggered by the Dix–Hallpike manoeuvre. Lateral canal canalolithiasis was diagnosed based on the following criteria: (1) and (2) as above, and (3) a direction-changing horizontal positional geotropic nystagmus in the right and left side head-down positions. Lateral canal cupulolithiasis was diagnosed based on the following criteria: (1) and (2) as above, and (3) a direction-changing horizontal positional apogeotropic nystagmus in the right and left side head-down positions. Mixed-type BPPV was diagnosed in cases of combined positional nystagmus of posterior canal and lateral canal BPPV. Patients with the sensation of vertigo, who were suspected of having BPPV but who did not have direction-changing positional nystagmus on head movement, were excluded from this study. All patients had their hearing checked using pure tone audiometry.

The posterior canal BPPV patients were divided into two groups according to the treatment methods. One group underwent the Epley manoeuvre[1] (194 patients, 84 per cent) and the other received medication (betahistine mesilate) (38 patients, 16 per cent). The lateral canal canalolithiasis patients were also divided into two groups according to the treatment methods. One group underwent the Lempert manoeuvre[2] (31 patients, 45 per cent) and the other received medication (38 patients, 55 per cent). Lateral canal cupulolithiasis patients (46 patients) were treated with medication and non-specific physical techniques, such as Brandt–Daroff exercises[3] or head shaking.

Patients with BPPV were then divided into three groups according to the prognosis: a curable BPPV group, a recurrent BPPV group and an intractable BPPV group. Recurrence was considered as the reappearance of symptoms after a symptom-free interval of more than 21 days. The follow-up period for checking recurrence was from one to six years. Intractable cases were those cases in which symptoms persisted for more than 60 days.

For statistical analysis, we used the Student's *t*-test; *p* values less than 0.05 were considered to indicate statistical significance.

Results

Patient age and gender

The ages of all BPPV patients ranged from 21 to 94 years, with an average age of 60 years. There were 114 men (31.9 per cent) and 243 women (68.1 per cent). The distributions of age and gender are illustrated in Figure 1.

Benign paroxysmal positional vertigo types

Posterior canal BPPV was diagnosed in 232 patients (65.0 per cent), lateral canal canalolithiasis in 69 patients (19.3 per cent), lateral canal cupulolithiasis in 46 patients (12.9 per cent) and mixed-type BPPV in 10 patients (2.8 per cent).

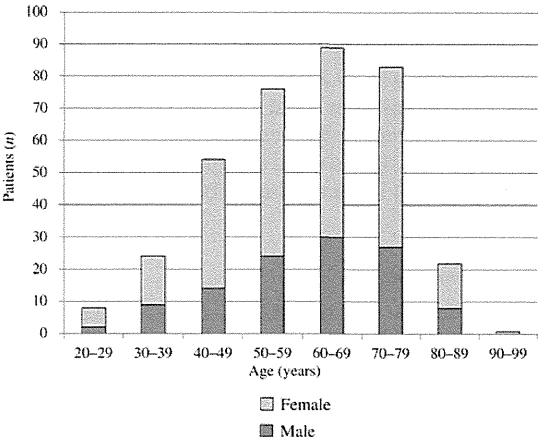

FIG. 1
Age and gender of patients with benign paroxysmal positional vertigo.

Average resolution time

The average period of time from initial consultation to resolution of symptoms in all BPPV patients was 13.8 days (Table I). For the posterior canal BPPV patients, the average resolution time was 9.6 days. The average resolution time was 7.7 days in the Epley manoeuvre group and 14.1 days in the medication group. The resolution time in the Epley manoeuvre group was significantly shorter ($p = 0.0010$).

For the lateral canal canalolithiasis patients, the average resolution time was 11.1 days. The average resolution time was 8.3 days in the Lempert manoeuvre group and 13.4 days in the medication group. The resolution time in the Lempert manoeuvre group was significantly shorter ($p = 0.0491$).

For the lateral canal cupulolithiasis patients, the average resolution time was 36.7 days. The resolution time in the lateral canal cupulolithiasis group was significantly longer than that in both the posterior canal BPPV group ($p = 0.0000$) and the lateral canal canalolithiasis group ($p = 0.0001$).

TABLE I
AVERAGE RESOLUTION TIME

Patient group	*n*	Days
All BPPV patients	357	13.8
Posterior canal BPPV	232	9.6
– Epley manoeuvre	194	7.7*
– Medication	38	14.1
Lateral canal canalolithiasis	69	11.1
– Lempert manoeuvre	31	8.3**
– Medication	38	13.4
Lateral canal cupulolithiasis	46	36.7

*$p = 0.0010$ versus the medication group. **$p = 0.0491$ versus the medication group. BPPV = benign paroxysmal positional vertigo

Curable group

The average age of the 284 patients in the curable BPPV group was 59.2 years. The BPPV types encountered were: posterior canal BPPV (193 patients, 68.0 per cent), lateral canal canalolithiasis (53 patients, 18.7 per cent), lateral canal cupulolithiasis (32 patients, 11.3 per cent) and mixed-type BPPV (6 patients, 2.1 per cent).

Recurrent group

The recurrence rate was 14.8 per cent. The average age of the 53 patients in the recurrent BPPV group was 61.3 years, which was not significantly different from that of the curable BPPV group. Types included: posterior canal BPPV (31 patients, 58.5 per cent), lateral canal canalolithiasis (15 patients, 28.3 per cent), lateral canal cupulolithiasis (5 patients, 9.4 per cent) and mixed-type BPPV (2 patients, 3.8 per cent). Although the percentage of lateral canal canalolithiasis cases was higher in the recurrent group than in the curable BPPV group, the difference was not significant.

Recurrence patterns

Recurrence involved the same canal in 27 patients (50.9 per cent), another ipsilateral canal in 12 patients (22.6 per cent) and the contralateral ear in 14 patients (26.4 per cent) (Figure 2).

Patient age and gender at recurrence

Fifty-three patients experienced a single recurrence, 11 experienced a second recurrence and 4 experienced a third recurrence. The average age at recurrence was 61.3 years at the first recurrence, 64.5 years at the second recurrence and 68.0 years at the third recurrence. In males, the incidence was 30.2 per cent at the first recurrence, decreasing to 18.2 per cent at the second recurrence and to 0 per cent at the third recurrence. In females, the incidence was 69.8 per cent at the first recurrence, increasing to 81.8 per cent at the second recurrence and to 100 per cent at the third recurrence. The average age of patients and the predominance for females increased in relation to the number of recurrences (Figure 3).

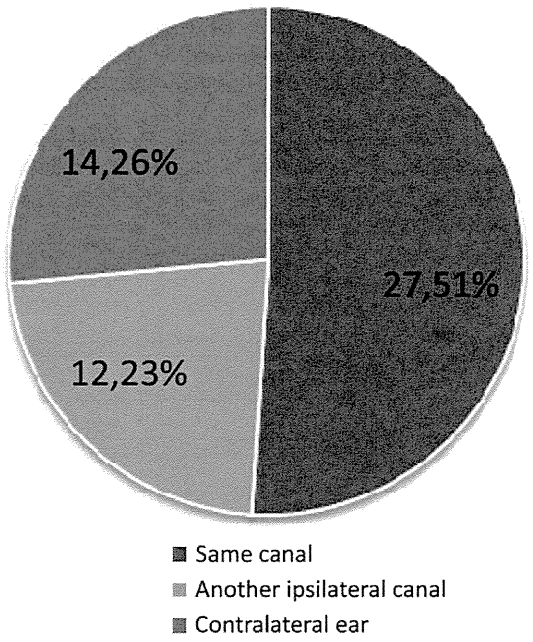

FIG. 2
Recurrence patterns.

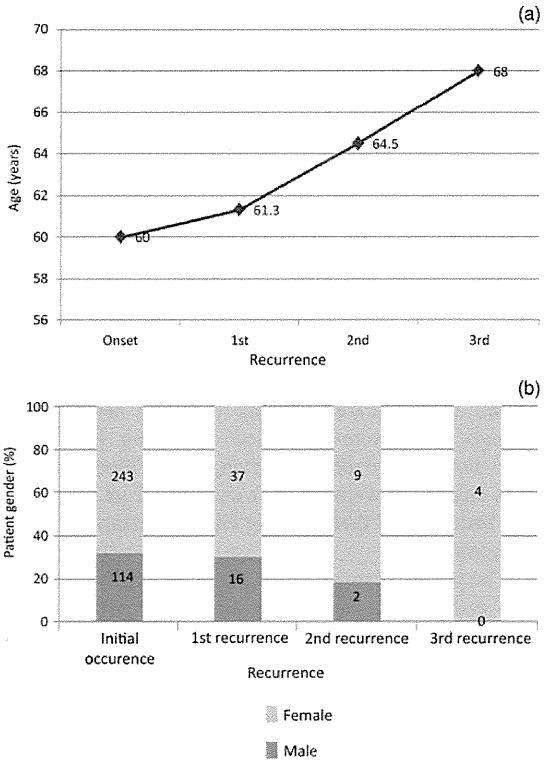

FIG. 3
Patient age and gender at time of recurrence.

Intractable group

Of the 357 BPPV patients, there were 20 intractable cases (5.6 per cent). The average age of the intractable group was 68.3 years, which was significantly higher than in the curable BPPV group ($p = 0.0023$). Of these 20 cases, 8 patients had posterior canal BPPV (40.0 per cent), 1 had lateral canal canalolithiasis (5.0 per cent), 9 had lateral canal cupulolithiasis (45.0 per cent) and 2 had mixed-type BPPV (10.0 per cent). The lateral canal cupulolithiasis group had a significantly higher rate of intractability than the curable BPPV group ($p = 0.0040$). The resolution period was over 100 days for 4 lateral canal cupulolithiasis patients.

Inner-ear function

Eleven (4 per cent) of 284 patients had sensorineural hearing loss (SNHL) in the curable BPPV group. Of the 53 recurrence cases, 3 (6 per cent) had SNHL, while 5 (25 per cent) of the 20 intractable cases had SNHL. Sensorineural hearing loss was more frequently associated with intractable BPPV than with curable BPPV ($p = 0.0004$).

Discussion

We set out to determine the clinical aspects and therapeutic strategies for BPPV. We reviewed 357 (9.4 per cent) patients diagnosed with BPPV (of 3797 vertigo patients treated over a 5-year period). Patients for whom a diagnosis of BPPV was only suspected were excluded from this study. If they had been included, the number of BPPV patients would have been more than doubled. In decreasing order of frequency, the types of BPPV encountered were: posterior canal BPPV, lateral canal BPPV and mixed-type BPPV. This is probably due to the anatomical location of the semicircular canals. If otoconial debris is dislodged, it tends to fall towards the back and bottom of the membranous labyrinth, where the posterior canal is located.

The Epley manoeuvre was performed on 84 per cent of patients in the posterior canal BPPV group, and the Lempert manoeuvre was carried out on 45 per cent of patients in the lateral canal canalolithiasis group. The Lempert manoeuvre was performed less than the Epley manoeuvre; this is because diagnosis of the affected side in lateral canal canalolithiasis cases is more difficult than in posterior canal BPPV cases. The average resolution time was significantly shorter in patients treated with the Epley manoeuvre than in those treated with medication ($p = 0.0010$). In addition, the average resolution time was significantly shorter for patients treated with the Lempert manoeuvre than for those treated with medication ($p = 0.0491$). The Epley and Lempert manoeuvres should be performed on patients who can tolerate the procedures well, and who do not have cervical spine problems or other conditions.

The average resolution time was significantly longer in cases of lateral canal cupulolithiasis than in the other types of BPPV. Lateral canal cupulolithiasis patients were treated by medication and non-specific physical techniques, such as the Brandt–Daroff exercises or head shaking. The findings of the present study suggest that these manoeuvres are not very effective for treating lateral canal cupulolithiasis.

We have previously performed model experiments using the membranous labyrinth of bullfrogs and confirmed the physiological validity of cupulolithiasis.[4] These experiments showed that the otoconia may not easily detach from the cupular surface in situations of cupulolithiasis. The cupula is mainly composed of mucopolysaccharide, which is very adhesive in nature. This adhesiveness makes the otoconia difficult to detach, resulting in intractable cupulolithiasis.[5] Physical therapy with maximal effectiveness for cupulolithiasis is required.

Kim *et al.* recently reported a new cupulolith repositioning manoeuvre with mastoid oscillation using a hand-held vibrator.[6] Symptoms were resolved in 62 per cent of the patients after 1 session and in 97 per cent of the patients after 6 sessions. The authors concluded that this manoeuvre was effective for lateral canal cupulolithiasis. We have previously investigated the kinds of stimuli that might be effective for detaching the otoconial mass from the cupula in experimental models of cupulolithiasis.[7] We concluded that vibration was the most effective method of detaching the otoconia from the cupula. We plan to examine the clinical efficacy of a mastoid oscillation manoeuvre in the treatment of lateral canal cupulolithiasis.

Various authors have reported different recurrence rates for BPPV, ranging from 7 to 50 per cent.[8–11] Our result was 14.8 per cent, which was within this range. Pérez *et al.* reported 19 cases of recurrence; of those, the recurrence rate in the same canal was 31.6 per cent, recurrence in another ipsilateral canal was 31.6 per cent and recurrence in the contralateral ear was 36.8 per cent.[12] These authors emphasised the importance of examining each canal in both ears, because BPPV is a syndrome that tends to relapse, rather than being a single entity that affects a particular side or canal. In our results (of the 53 patients with recurrence), recurrence in the same canal was around 50 per cent, while recurrence in another ipsilateral canal was about 25 per cent and recurrence in the contralateral ear was around 25 per cent (Figure 2). We contemplated that the otoconia tended to be detached from the same utricle and moved into the same semicircular canal while maintaining head position during sleeping or head movement during everyday activity. On the other hand, the otoconia detached from the contralateral utricle only occasionally.

As the number of recurrences increased, the average age of patients and the predominance in females increased (Figure 3). Brandt *et al.* also reported that women were more likely to experience recurrence than men.[9] It has been speculated that the decrease of oestrogen during and after menopause affects calcium metabolism, leading to detachment of the otoconia from the utricle. Oestrogen plays an important role in otoconial metabolism. After ovariectomy, the density of otoconia has been reported to decrease and the size of the otoconia increases.[13] In adult animals, the number of otoconia and concentration of calcium decreases.[14] Motohashi *et al.* reported that oestrogen receptors were expressed in the inner ear (i.e. in the outer and inner hair cells, spiral ganglion cells, vestibular ganglion cells, dark cells and endolymphatic sac), and that these expressions decrease with increasing age.[15] This finding suggests that a decreased oestrogen receptor level of the dark cells in aged animals leads to changes in otoconia. The rapid decrease in the

oestrogen level in menopause causes a decrease in the number of oestrogen receptors, which may induce a disturbance in the otoconial metabolism.

The average age of patients was significantly higher in those with intractable BPPV compared with curable BPPV patients ($p = 0.0023$). The rate of SNHL was also significantly higher in patients with intractable BPPV than in curable BPPV patients ($p = 0.0004$). Both the ageing process and SNHL may be associated with ischaemia. Four of the lateral canal cupulolithiasis patients had a resolution time of over 100 days. It is difficult to explain the mechanism of this long resolution time simply based on the effects of cupulolithiasis. We speculate that the cupula may sustain morphological damage from ischaemia, such as shrinkage.

- **For posterior canal benign paroxysmal positional vertigo (BPPV) cases, resolution time was shorter following Epley manoeuvre versus medication**
- **For lateral canal canalolithiasis cases, resolution time was shorter following Lempert manoeuvre versus medication**
- **Resolution time was longer for the lateral canal cupulolithiasis group than other BPPV types**
- **Average patient age and female predominance increased with the number of recurrences**
- **Average patient age and sensorineural hearing loss rate were higher for intractable BPPV cases**

Research suggests that the cupula shrinks under various conditions.[16–18] Konomi *et al.* reported that the cupula shrank after a gentamicin injection into the inner ear, with or without damage to the sensory cells.[16] It is expected that the movement of the cupula will change as it shrinks. Kondo *et al.* observed similar cupular changes after puncturing the membranous labyrinth.[17] The cupula was also found to change in a high osmolarity environment.[18] In addition, cupular change was revealed in our ischaemia model.[18] The cupula is fragile, and change is induced easily as a result of various insults, including SNHL and other inner-ear diseases. Maintaining a favourable inner-ear condition for calcium metabolism should help to prevent recurrence and intractability of BPPV.

This study had the limitation of being retrospective and was conducted at a single institution only.

Conclusion

For the posterior canal BPPV patients, the resolution time was significantly shorter in the Epley manoeuvre group than in the medication group. For the lateral canal canalolithiasis patients, the resolution time was significantly shorter in the Lempert manoeuvre group than in the medication group. The resolution time was significantly longer in the lateral canal cupulolithiasis patients than in the other BPPV patients. As the number of recurrences increased, the average age of patients increased as did the predominance in females. The average patient age and the rate of SNHL were significantly higher in those with intractable BPPV compared with the curable BPPV patients.

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Address for correspondence:
Dr K Otsuka,
Department of Otolaryngology,
Tokyo Medical University,
6-7-1 Nishi-shinjuku,
Shinjuku-ku,
Tokyo 160-0023, Japan

Fax: +81-(0)3-3346-9275
E-mail: otsukaent@aol.com

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Auditory-pupillary responses in patients with vestibular neuritis

Naoharu Kitajima*, Noriko Kobayashi, Koji Otsuka, Yasuo Ogawa, Taro Inagaki, Akihide Ichimura and Mamoru Suzuki
Department of Otolaryngology, Tokyo Medical University, Tokyo, Japan

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Abstract. Pupillary dilation in response to sound stimuli is well established and generally represents a startle reflex to sound. We previously reported that auditory-pupillary responses (APRs) persist with bilateral deafness, and that the pathways mediating APRs involve not only the cochlea but also otolith organs, especially the saccule. Here, we evaluated the vestibulo-autonomic responses in vestibular neuritis (VN) by assessing APRs. Twelve young healthy volunteers without a history of hearing and equilibrium problems and 10 VN patients participated. To clarify the relationship between APRs and vestibular function, especially otolith function, we performed caloric and vestibular-evoked myogenic response testing on VN patients. In normal subjects, we examined APRs when delivering sound stimuli to both sides. In VN patients, we examined APRs when delivering stimuli simultaneously to both sides, to the affected side alone, and then to the unaffected side alone. With binaural stimulation, the pupillary index (PI) – the rate of dilation – of VN patients significantly differed from those of normal subjects. Moreover, in VN patients, PIs of the affected sides were significantly larger than those of the unaffected sides. Our study provides evidence that examining APRs may be useful for evaluating vestibulo-autonomic reflexes, especially otolith-autonomic reflexes.

Keywords: Auditory-pupillary response, vestibulo-autonomic response, vestibular neuritis, otolith function

1. Introduction

Pupillary dilation in response to sound stimuli is well established [24], and is generally considered to represent a startle reflex to sound, especially sounds related to emotions. This phenomenon is called the auditory-pupillary response (APR) [9]. We previously reported that APRs persist in patients with bilateral deafness [8]. We hypothesize that APRs represent not only a simple startle reflex to sound stimuli but may also represent a reaction to stimulation of other sense organs. In other words, APRs may involve not only auditory stimulation of the cochlea but also that of the otolith organs, especially the saccule. These findings led us to the notion that examining APRs may be useful for evaluating vestibulo-autonomic reflexes.

Therefore, in present study, we used APRs to examine the vestibulo-autonomic reflexes of patients with vestibular neuritis (VN), a form of peripheral disequilibrium. Generally, VN is paroxysmal vertigo that can last for several hours to a few days, as in the patients of this study. In the acute phase, it may be associated with nausea and vomiting; that is, a particular type of autonomic dysfunction. Most patients experience complete recovery within a few weeks. VN is diagnosed using three clinical diagnostic criteria [4]: (1) vertigo, which is usually sudden onset; (2) absence of cochlear signs and symptoms such as deafness and tinnitus; and (3) absence of associated neurological signs and symptoms. By definition, VN patients do not show cochlear signs or symptoms. Therefore, we concluded that we did not need to consider any decreases in APRs due to hearing loss and could simply determine whether

*Corresponding author: Naoharu Kitajima, Department of Otolaryngology, Tokyo Medical University, 6-7-1 Nishishinjuku Shinjuku-ku, Tokyo 160 0023, Japan. Tel.: +81 3 3342 6111; Fax: +81 3 3346 9275; E-mail: nao-ake@bk2.so-net.ne.jp.

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Table 1
Pupillary response data for normal subjects

Subject no.	Age (y)	Sex	Baseline pupillary diameter (mm)	M1 (msec)	D1 (msec)	P1I
1	35	M	2.04	370	700	2.94
			2.16	330	670	2.78
2	31	F	2.20	430	630	3.64
			2.36	430	630	3.39
3	28	M	2.32	400	630	2.59
			2.38	430	630	2.52
4	26	F	2.30	270	930	7.83
			2.32	300	870	7.76
5	26	M	1.80	370	670	6.67
			2.02	400	730	6.93
6	26	F	†	†	†	†
			2.48	370	700	6.45
7	33	M	1.78	370	700	4.49
			1.96	370	700	4.08
8	35	F	†	†	†	†
			2.02	300	700	2.97
9	26	M	†	†	†	†
			2.50	130	600	5.60
10	41	M	4.28	430	870	13.08
			4.80	330	870	12.50
11	42	F	2.72	230	1070	7.35
			2.84	300	1170	5.63
12	28	F	2.84	430	1300	7.04
			3.52	370	1170	7.95

†Parameters were technically difficult to measure. For each subject, the first column contains right eye data and the second column contains left eye data.

vestibular dysfunction and APRs are correlated. The present study was undertaken to evaluate the vestibulo-autonomic responses in VN using APRs and to clarify the relationship between APRs, canal paresis (CP), and vestibular-evoked myogenic potentials (VEMPs).

2. Methods

The participants were 12 healthy volunteers (6 males and 6 females; age range of 26–41 years; mean ± SD of 31 ± 6 years) without a history of hearing and equilibrium problems and 10 patients with VN (5 males and 5 females; age range of 33–74 years; mean ± SD of 57 ± 14 years) (Tables 1 and 2).

To make a definite diagnosis of VN, we tested the patients for VN. All patients underwent hearing tests (pure-tone audiometry) and were checked for the absence of cochlear signs and symptoms. Generally, a reduced or absent response in the caloric test is not a necessary criterion for the diagnosis of VN. However, to make a diagnosis of VN in Japan, CP is an essential criterion; thus, we tested all patients with the caloric test. If the CP% was more than 25%, the subject was diagnosed as having CP. In addition, to clarify the relationship between APRs and otolith function, we performed a vestibular-evoked myogenic response test on the patients by assessing their VEMPs. The procedure for carrying out and analyzing VEMPs were previously reported [2]. For recording VEMPs, 100 dB nHL clicks (0.1 ms) generated by a Neuropack ∑ evoked-response measuring system (MEB-5500; Nihon Koden, Japan) were presented to each subject through headphones (DR-531; ELEGA, Japan).

APRs of both eyes were assessed using computer pupillography. Testing was performed with a binocular infrared pupillograph designed and built at our institute [8]. After exposure to auditory stimuli, pupil size was measured with an infrared electronic ocular measurement device (NewOpt, Kawasaki, Japan) and a data processor (NewOpt) in tandem with a portable computer (Windows XP). Auditory stimuli consisted of impulsive stimuli or clicks. Click stimuli were rarefactive square waves (duration: 0.1 ms; intensity: 100 dB nHL) generated by a Neuropack ∑ evoked-response measuring system. Tone bursts were not used. The stimuli were delivered through calibrated headphones (DR-531; ELEGA, Japan). In normal subjects, we examined APRs when delivering sound stimuli to both sides. In VN patents, we examined APRs with sound stimuli delivered to both sides, to the unaffected side alone, and to the affected side alone. Otherwise, all testing was carried out under conditions identical to those described in our previous study [8].

Table 2
Neurotological data of VN patients

Patients no.	age (y)	sex	Time elapsed between onset and each test (days)	CP%	VEMP	Auditory pupillary responses											
						Both ears stimulated				Affected ear stimulated				Unaffected ear stimulated			
						Baseline pupillary diameter (mm)	M1 (msec)	D1 (msec)	PH	Baseline pupillary diameter (mm)	M1 (msec)	D1 (msec)	PH	Baseline pupillary diameter (mm)	M1 (msec)	D1 (msec)	PH
1	66	F	9	100	Irregular	3.23	570	970	7.43	2.86	330	870	13.99	3.32	130	800	8.43
					Normal	3.64	570	1030	4.40	3.16	300	900	8.86	3.60	530	900	5.56
2	41	F	33	100	Normal	2.54	370	1070	6.30	2.48	530	1300	8.87	2.30	330	1030	6.96
					Normal	2.30	300	1030	8.70	2.16	500	1400	11.11	2.10	330	1300	9.52
3	54	M	29	100	Normal	2.50	270	770	6.40	2.30	230	770	6.09	2.50	300	730	7.21
					Normal	2.24	270	730	8.93	2.16	300	730	7.41	2.22	370	730	4.80
4	70	F	44	100	Normal	1.72	430	1330	9.30	†	†	†	†	†	†	†	†
					Normal	2.28	530	1130	5.26	2.20	500	930	7.27	2.24	430	800	5.36
5	47	M	4	67	Irregular	2.18	200	700	11.01	2.52	230	830	6.35	2.34	530	1170	10.26
					Normal	2.60	200	870	8.46	2.90	230	800	4.83	2.76	470	1000	5.80
6	33	F	144	44	Normal	2.52	900	1030	7.94	2.54	170	1000	7.09	2.46	400	1070	7.32
					Normal	2.62	470	1030	6.11	2.24	170	870	11.61	2.48	300	970	6.45
7	57	F	22	33	†	2.12	470	970	13.21	2.04	400	900	11.76	2.20	300	870	10.91
						†	†	†	†	†	†	†	†	†	†	†	†
8	71	M	28	31	–	3.72	470	1070	7.53	3.54	470	1000	6.78	3.78	300	930	5.29
						3.24	470	1070	6.17	3.22	430	1000	6.21	3.42	370	800	4.68
9	74	M	4	25	Normal	1.82	400	800	7.69	1.76	370	1000	6.82	1.78	400	900	5.62
					Normal	1.60	430	800	6.25	1.52	370	1030	7.89	1.56	420	930	5.13
10	61	M	44	25	Normal	1.72	400	900	11.63	1.96	330	830	9.18	1.84	300	830	6.52
					Normal	2.32	370	870	10.34	2.24	420	930	8.04	2.32	530	1000	4.31

† Parameters were technically difficult to measure. For each patient, the first column contains eye data for the affected side and the second column contains eye data for the unaffected side. Each test was carried out at almost the same time.

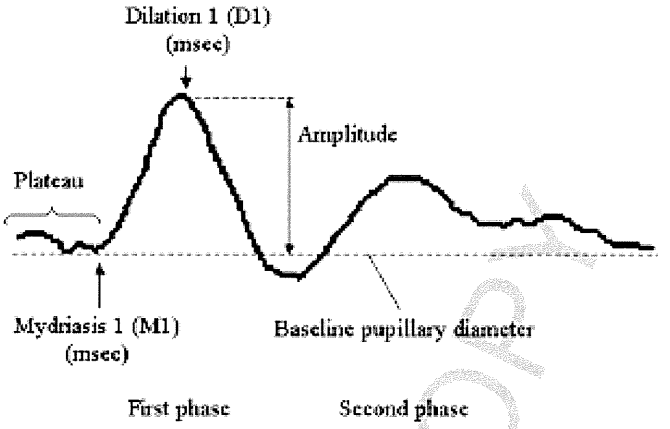

Fig. 1. Components of the auditory-pupillary response. Analysis involved averaging the response data with a portable computer. Once the data were averaged, we measured the baseline pupillary diameter (dotted line); latency of the initial mydriasis before the appearance of the first phase curves (M1); and dilation 1 (D1), the dilation that occurs during this phase. The amplitudes of the first phase curves were then converted into a pupillary index (PI 1) and analyzed.

Responses were assessed according to the following criteria (Fig. 1): (1) The response curves were not contaminated by irregular curves caused by nystagmus, blinking, or pupillary oscillations; (2) the baseline pupillary diameter remained largely unchanged. We excluded pupillary-diameter data obtained immediately at the start of sound stimulation. In other words, response curves, by definition, were preceded by a plateau.

We defined pupillary index (PI) as follows: $PI = (amplitude/baseline\ pupillary\ diameter) \times 100$.

When biphasic APR response curves were obtained, it was difficult to measure the second phase, especially mydriasis 2 (M2), because of physiological pupillary oscillations. Therefore, we measured only the first phase – mydriasis 1 (M1) and dilation 1 (D1) – and then calculated PI (that is, PI1).

This study was conducted in accordance with the ethical principles in the Declaration of Helsinki. All procedures were carried out with adequate understanding of the subjects and written consent and were approved by the review board of Tokyo Medical University (No. 802).

We compared the results obtained from the normal subjects and VN patients. Calculations were performed with Stat Mate IV software (Atoms, Japan). The Mann-Whitney U test and Pearson product-moment correlation coefficient were used for statistical analysis. $P < 0.05$ was considered significant.

3. Results

APRs of the left and right eyes were nearly equal (Tables 1 and 2). Across all VN patients and normal subjects, the above-described criteria were met in 10–12 traces of 20 recordings. These recordings were averaged and analyzed.

The APRs result with sound stimuli delivered to both sides are described next. In normal subjects, the mean ± SD baseline pupillary diameter was 2.47 ± 0.68 mm (n = 12 subjects, 21 eyes). All subjects responded to auditory stimulation. The mean M1 was 350.5 ± 76.5 msec, ranging from 300.0 to 430.0 msec (n = 12, 21 eyes). The mean D1 was 806.7 ± 208.8 msec, ranging from 630.0 to 1300.0 msec (n = 12, 21 eyes). The mean PI1 was 5.91 ± 2.98, ranging from 2.52 to 13.08 (n = 12, 21 eyes) (Table 1). On the other hand, in VN patients, the mean baseline pupillary diameter was 2.47 ± 0.61 mm (n = 10 subjects, 19 eyes). All of the VN patients responded to auditory stimulation. The mean M1 was 404.7 ± 113.4 msec, ranging from 200.0 to 570.0 msec (n = 10, 19 eyes). The mean D1 was 956.3 ± 157.9 msec, ranging from 700.0 to 1330 msec (n = 10, 19 eyes). The mean PI1 of VN patients was 8.06 ± 2.29 (n = 10, 19 eyes), which was significantly larger than that of normal subjects ($P < 0.05$) (Table 2).

When the affected side was stimulated alone, the mean baseline pupillary diameter was 2.43 ± 0.53 mm (n = 10, 18 eyes). All VN patients responded to au-

Table 3
Auditory-pupillary responses (APRs) following sound stimulation

		Both ears stimulated	Affected ear stimulated	Unaffected ear stimulated
APRs	Eyes on affected side	8.84 ± 2.36	8.55 ± 2.73	7.61 ± 1.93*
(PI1)	Eyes on unaffected side	7.18 ± 1.96	8.14 ± 2.16	5.73 ± 1.56*

*$p = 0.02$ We compared APRs and PI1 values recorded from eyes of the affected side with that from eyes of the unaffected side.

ditory stimulation. The mean M1 was 348.9 ± 113.8 msec, ranging from 170.0 to 530.0 msec ($n = 10$, 18 eyes). The mean D1 was 949.4 ± 170.1 msec, ranging from 730.0 to 1400.0 msec ($n = 10$, 18 eyes). The mean PI1 was 8.34 ± 2.40 ($n = 10$, 18 eyes) (Table 2). When the unaffected side was stimulated alone, the mean baseline pupillary diameter was 2.51 ± 0.63 mm ($n = 10$, 18 eyes). All patients responded to auditory stimulation. The mean M1 was 374.4 ± 102.8 msec, ranging from 130.0 to 530.0 msec ($n = 10$, 18 eyes). The mean D1 was 929.4 ± 151.2 msec, ranging from 730.0 to 1330.0 msec ($n = 10$, 18 eyes). The mean PI1 was 6.67 ± 1.96 ($n = 10$, 18 eyes). The PI1 of the stimulated affected side was significantly larger than the PI1 of the unaffected side ($P < 0.05$) (Table 2). The mean CP% was 62.5 ± 34.4%, ranging from 25.0% to 100.0% (i.e., complete CP) ($n = 10$). Nine VN patients underwent VEMP testing. In one patient (no. 7), however, VEMPs was technically difficult to measure. Six patients had normal VEMPs and 2 patients had irregular VEMPs in the affected side. CP% was not significantly correlated with PI1. The period of time between the onset of vertigo and each examination was 36.1 ± 40.7 days, ranging from 4 to 144 days.

Table 3 shows the APRs recorded after sound stimulation. Comparison of PI1 values revealed that for each type of sound stimuli, PI1 values recorded from eyes of the affected side tended to be larger than those recorded from eyes of the unaffected side. This was especially clear when the unaffected ear received stimulation: PI1 values of eyes of the affected side were significantly larger than those of the unaffected side ($p = 0.02$).

4. Discussion

In our previous study, we described vestibular stimulation-related APRs [8]. Generally, APRs are thought to be related to auditory function [18]. However, Nishida et al. reported that pupillary responses are also closely related to vestibular function [16]. Therefore, we initially hypothesized that APRs in VN patients with vestibular dysfunction might be weaker than APRs in normal subjects. Surprisingly, APRs in VN patients are significantly larger than those in normal subjects. Moreover, APRs recorded from the affected side were significantly stronger than those from the unaffected side. In the present study, APRs were robust despite the presence of CP. We initially expected that the extent of CP would affect the APRs. However, there was no correlation between CP% and PI1. These results suggest that the pathway(s) underlying APRs mainly receive inputs not from the semicircular canals but from another organ, for example, otolith organs such as the saccule.

The vestibular system has long been known to play an important role in autonomic control. Thus, it is not surprising that the autonomic nervous system would be affected by vestibular dysfunction. Indeed, many investigators have reported autonomic nervous system dysfunction in patients with vertigo [1,5,10,17,20,22, 23]. Several studies have suggested that asymmetry in the autonomic nervous system in vertiginous patients causes asymmetrical excitability of the vestibular system, resulting in nystagmus and vertigo [19, 21]. Moreover, the same studies found a correlation between asymmetry in the autonomic nervous system and side differences in vertebrarterial flow [19,21]. We observed that after sound stimulation APRs recorded from the affected side were larger than those from the unaffected side (Table 3). This may be due to asymmetry in the autonomic nervous system.

According to Kawasaki [7], decreased parasympathetic activity and suppression of sympathetic responses are present in vertiginous patients. The first phase of the response occurs as a result of inhibition of the parasympathetic nervous system [6]. In patients with CP, vestibular dysfunction might cause decreased parasympathetic activity in the affected side, thereby causing APRs in the affected side to be larger than those in unaffected side. Hence, APRs might be affected by CP indirectly.

In our previous study, we proposed that cells involved in APRs mainly receive inputs from otolith organs, especially the saccule, because the saccule is the most sound-sensitive vestibular end organ [2,11,14,15] and because the APR threshold was close to the VEMP threshold [10]. In the study of Murofushi et al., 34% of VN patients lacked unilateral VEMPs [12]. They