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PERSISTENT GEOTROPIC NYSTAGMUS - A DIFFERENT KIND OF CUPULA PATHOLOGY

av

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Life gives back to us only what we give to others.

Ivo Andric

ABSTRACT

In patients with positional vertigo a persistent positional direction-changing nystagmus (PDCN) of *apogeotropic* direction (a-PDCN) in the supine yaw plane has been described earlier [1-5]. It has been suggested that the cupula in the lateral semicircular canal has a higher specific weight than the surrounding endolymph making the cupula sensitive to gravity. This condition is known as ”heavy cupula”. We have described, in Paper I, a *geotropic* persistent direction-changing nystagmus (g-PCDN) in patients during vestibular crisis[6]. In addition, when the patient is in the supine position and the head is turned slowly from one side to the other it is possible to discern a zero zone where the geotropic nystagmus is absent. This is accomplished when the head is turned circa 10-20 degrees laterally. Theoretically this occurs when the longitudinal axis of the affected cupula is aligned with the gravitational vertical [7-9].

On the assumption that a position dependent nystagmus such as persistent a-PDCN is caused by a heavy cupula in one of the lateral semicircular canals (LSCC), thus it could be hypothesized that a g-PDCN can be caused by the cupula that is lighter than the surrounding endolymph. We have called this new diagnostic entity “light cupula”.

A similar phenomenon of a PDCN is seen in subjects with positional alcohol nystagmus (PAN) [10-18]. This phenomenon is based on the” buoyancy hypothesis”[19,20]. In order to reproduce a clinical condition where the density of the cupula was lower or higher than the surrounding endolymph we examined the nystagmus pattern in different head positions in unilaterally deafferented patients during the stage of PAN 1 and PAN 2 respectively[21,22].

We compared results of nystagmus direction during PAN 1 (Paper II) with the findings in patients with light cupula in the LSCC (Paper I). Nystagmus direction in both supine and prone lateral head positions was compatible with that of a light cupula. However, the nystagmus directions at head straightforward in prone and supine position as well as the localization of zero zones deviated from the pattern seen in patients with a light cupula[21].

We followed up nystagmus characteristics and nystagmus pattern in Paper III on the labyrinthectomized subjects during the stage of PAN 2[22]. This study showed persistent a-PDCN according the theory [12]. The nystagmus pattern in pitch plane was of opposite to that during PAN 1. Nystagmus in supine position was directed to the affected side during PAN 2 and to non-affected side during PAN 1 but the zero zones in both studies is found on the affected side.

We were interested to see if the results concerning the nystagmus pattern in the experimental studies could be applied to patients during vestibular disability with g-PDCN permitting a lateralization of the affected side. In Paper IV we examined an extended series of 20 patients with g-PDCN nystagmus pattern during acute vestibular disability and at follow up 1-7 years later. Nystagmus patterns in different head positions were recorded, both caloric and otolith tests were carried out. Concomitant auditory symptoms as an indication of the affected side were rare. The slow phase velocity (SPV) of geotropic nystagmus was low and of equal intensity and did not present an indication of the affected side according to Ewald´s second law[23]. With nystagmus analysis we found evidence for a cupula that is sensitive to gravitation, but did not find an applicable pattern for simply determination of the affected side by analysing nystagmus direction in the pitch plane and in lateral head positions. There was a high prevalence of migraine (40%) and the patients also had problems with recurrent vertigo (80%). The vestibular tests were pathologic in 60% of the patients.

CONTENTS

LIST OF PUBLICATIONS

This thesis is based on the following original papers.
They will be referred to the text by their Roman numerals I-IV.

I. Bergenius J, Tomanovic T. Persistent geotropic nystagmus--a different kind of cupular pathology and its localizing signs. Acta Otolaryngol. 2006 Jul; 126: 698-704

II. Tomanovic T, Bergenius J. Can the nystagmus pattern in patients with a 'light cupula' be reproduced in hemi-labyrinthectomized subjects during positional alcohol nystagmus 1? Acta Otolaryngol. 2011 Sep; 131: 929-936.

III. Tomanovic T, Bergenius J. Is the nystagmus pattern in hemi-labyrinthectomized subjects during positional alcohol nystagmus 2 similar to that found in patients with cupulolithiasis in the lateral semicircular canal? Acta Otolaryngol. 2013 Aug; 133: 796-803.

IV. Tomanovic T, Bergenius J. Vestibular findings in patients with persistent geotropic positional nystagmus: the “light cupula” phenomenon. Submitted for publication in 2014.

LIST OF ABBREVIATIONS

PN	Positional nystagmus
SPV	Slow phase velocity
g-PDCN	Geotropic persistent direction changing nystagmus
a-PDCN	Apogeotropic persistent direction changing nystagmus
VOR	Vestibulo-ocular reflex
PAN	Positional alcohol nystagmus
c-VEMP	Cervical vestibular evoked myogenic potential
o-VEMP	Ocular vestibular evoked myogenic potential
SVH	Subjective visual horizontal
CNS	Central nervous system
BPPV	Benign Paroxysmal Positional Vertigo
GSD	Geotropic side difference
SCC	Semicircular canal
VNS	Video-nystagmoscopy

THESIS SUMMARY

Foreword

The vestibular system provides the information about body position that allows rapid compensatory movements in response to forces generated internally and externally. We are normally unaware of its function. If the system is damaged, balance, eye movements and sense of orientation in space are affected. Hence, it is important to elucidate the different conditions that lead to a disturbance in this complex system. The main symptom of disturbance in the vestibular system is dizziness and unsteadiness. Dizziness can be provoked by changes in head or body position causing positional dizziness, which can be confirmed by positional nystagmus (PN). One of the subtypes of PN is persistent g-PDCN. This thesis is based on clinical and experimental studies, which aim to describe the nystagmus characteristics and pathophysiological mechanisms of vestibular disability with persistent g-PDCN that we have named "light cupula".

INTRODUCTION

Historical background

At the beginning of the last century Robert Barany studied positional nystagmus[24]. He found a noticeable connection between positional nystagmus and the gravitational forces.

Carl Olof Nylén carried out studies [25] devoted to classification and definition of positional nystagmus. He stated that the positional nystagmus is altered when the head adopts another position and in his classification there are three main types of positional nystagmus:

- Direction-changing, changing direction in different positions of the head
- Direction fixed, beating always to the same direction
- Irregular, characterized by variations in its behavior.

He stated, "The probability is that both the peripheral and central system are capable of giving rise to positional nystagmus". With peripheral affection it is conceivable that positional nystagmus arises through deficient interplay of the otoliths and the cupula due to the fact that experimentally nystagmus occurs, with stimulation of the cupula but not with stimulation of the otolith organ.

Aschan et al. have studied positional nystagmus in man mainly the persistent form [11,12,26,27]. Their investigation indicated that the position of the head is a determining factor in the persistent form of positional nystagmus, but in the transitional forms of nystagmus, movement of the head plays a significant role. Stenger in 1955 [28] further emphasized the classification of positional nystagmus into two types caused by:

- Position itself
- Changes in position

In 1952, Dix and Hallpike described torsional vertical nystagmus provoked by a specific ear-down position with a latency of several seconds, in which the nystagmus lasted only for a limited time, usually less than 20 seconds, and the direction of the nystagmus reversed on resuming the upright position. The nystagmus also showed fatigability with a progressive decline in intensity on repetition of these manoeuvres [29,30]. These authors coined the term "benign paroxysmal positional vertigo" (BPPV), and the provocative positional testing was named in their honour.

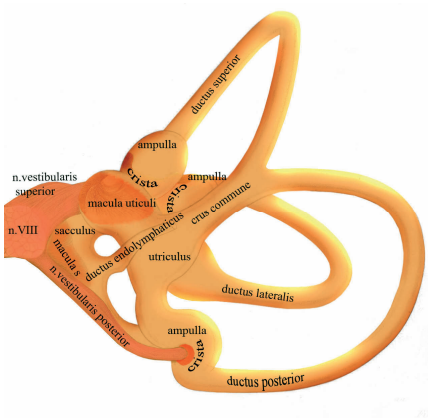
Schuknecht was the first to provide a pathophysiological concept of BPPV [31,32]. In 1969 he proposed the theory of "cupulolithiasis" on the basis of pathological studies that demonstrated otolithic debris attached to the cupula. However, the concept of cupulolithiasis has several limitations and is thus unable to explain all of the characteristics of nystagmus and vertigo in BPPV [33]. In 1979, Hall and al. and then other researchers put forward a new explanation for the transient vertigo in patients BPPV. It was suggested that BPPV was caused by particles floating around in the endolymph [34-36]. As they are heavier than the surrounding endolymph they are subject to the influence of gravity. Due to fast head movements or long lasting positions of the head they will precipitate and assemble in the semicircular canals.

Semont et al. referred to physical therapy as a liberatory manoeuvre [37]. In 1992 Epley reported his first results in curing positional vertigo by physical therapy referred it as the “canalith repositioning procedure”[38]. Both techniques are for relocation of the particles from the posterior semicircular canal (PSCC). Since that time, specific physical therapy has been widely applied to patients suffering from BPPV [39]. Prior to the 1985 it was believed that BPPV developed only in the PSCC [40-42]. However, in 1985 McClure introduced the concept and clinical features of BPPV involving the lateral semicircular canal (LSCC) without any evidence of central lesions[43,44]. He reported patients with horizontal geotropic nystagmus precipitated by head movements in supine position into or out of one of the lateral positions. In 1995, Baloh et al. reported three patients in whom the nystagmus changed direction in each lateral head position always beating away from the ground. This positional nystagmus had all of the features usually ascribed to a central lesion; no latency, no fatigability and persisted as long as the position was held. They proposed that nystagmus was result of debris attached to the cupula of the LSCC [3,4,45]. Particle movement in the LSCC was also suspected as a pathophysiological substrate and hence different types of physical therapy were recommended [38,46-48]. There are mainly three different types of positional nystagmus: vertical torsional paroxysmal, geotropic direction-changing paroxysmal, and apogeotropic direction-changing persistent, all result from debris in different parts of the inner ear [3,49-52].

Posterior canal BPPV is the most frequently reported form of BPPV, about 60-80%[53-55] of cases. Lateral canal BPPV accounts for approximately 10-20% and the anterior SCC is affected in 1-2 %[56-58] of cases. Other rare variations include paroxysmal apogeotropic canalolithiasis of the LSCC [59,60], direction fixed BPPV in LSCC [61], cupulolithiasis of PSCC [62,63], g-PDCN [6] and multiple canal BPPV [64,65].

Vestibular apparatus

Figure 1. The labyrinth and its innervations



The vestibular system consists of a peripheral part located in the inner (Figure 1) ear and integrative centers located in the brainstem, cerebellum and somatic sensory cortices. The vestibular part of inner ear is situated posterior to the cochlea and consists of the bony labyrinth, containing the fluid perilymph, and the membranous labyrinth. The membranous labyrinth is a system of thin-walled sacks and ducts filled with endolymph. Five vestibular receptor organs contain highly organized sensory hair cells and supporting cells were gathered in two otolith maculae, the utriculus and the sacculus, and three crista ampullaris, in each SCC. The otolith organs, utriculus and sacculus represent a set of three-dimensional linear accelerometers that detect gravitational and translational components associated with any head movement. The three pairs of SCCs represent a set of three-dimensional angular accelerometers to detect the head angular velocity.

The membranous labyrinth is filled with endolymph; the sodium (Na+) content is low, and the potassium (K+) content is high, which causes the endolymph to resemble intracellular rather than extracellular fluid. The dark cells of the cristae and maculae presumably produce endolymph and the site of absorption of endolymph is presumably the endolymphatic sac[66,67].

Otolith organs

Neuroepithelium of the macula sacculi and macula utriculi is covered by an extracellular mass- otoconial membrane, which consists of thousands of otoconia about 1-5 μm long. The otoconial membrane is composed of type II collagen, glycoproteins, and proteoglycans that maintain the calcium crystal content and hold it to the sensory epithelium. The otoconial mass is held together by beaded filaments and attached to a gelatinous matrix or so-called globular substance that actually generates the calcium carbonate crystals. The kinocilium of the utriclar macula is set into pores of the otoconial membrane, on which the otoconia are densely distributed[68,69]. Linear acceleration (in the three dimensions), including tilting of the head (in the roll and pitch plane), causes the otoconial mass to move and thereby bend the kinocilium and stereocilia of the hair cells, evoking a change in the firing rate through the vestibular nerve. In animal studies of elderly mice, the otoconia have become demineralized resulting in weakening or loss of anchoring of the fibrils interconnecting the otoconia [70].

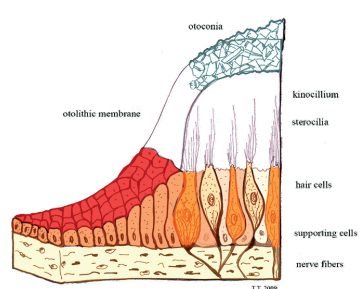


Figure 2. Cross section of the utricular macula

As a result of the aging process, trauma, inflammation, and perhaps other factors, calcite crystals may dislodge from the otolithic membrane and sink into the endolymph fluid. Old are

replaced by new growing otoconia. Reabsorption of free otoconia by the dark cells takes at least 100 hours in mice [71].

Semicircular canals

From the utriculus, arise three curved membranous tubes, the superior, the lateral and the posterior semicircular ducts, named according to their orientation in space. Each duct communicates at both ends with the utriculus. Every canal begins independently but only the lateral canal ends independently to the utriculus. The posterior and superior canals have a common limb or crus commune, which simply emerge into the utriculus. Each SCC consists of a toroidal loop of fluid including an enlarged ampulla where the sensory epithelium resides on a crista.

The SCC are responsible for sensing angular motion of the head around three axes and provide afferent signals critical to the neural control of balance, posture, and stabilization of the visual image on the retina. There is an x-axis, which refers to rotation as a roll; the imaginary axis goes through the sagittal plane. The y- axis goes through the horizontal plane and rotation is called pitch. The z-axis is orientated through frontal plane and rotation is called yaw.

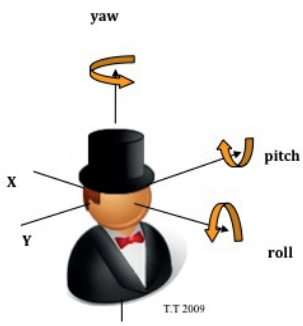


Figure 3. The three degrees of rotational freedom refer to a body`s rotation relative to the x, y and z axes and are commonly referred to as roll, pitch and yaw

Endolymph displacement within the 3 canal labyrinth is responsible for decomposing the three dimensional directions of angular head motion into three separate vectors associated with the planes of each SCC. Two canals on the each side work together in the pull-push arrangement[72]. A single canal is maximally stimulated when rotated its plane, the optimal head position plays roll for rotational and caloric stimulation [73].

Further orientation angles are given in Read stereotaxic coordinate system. This system defines the horizontal plane as one passing through the inferior margin of the orbitals and the centre points of the two external auditory canals. The lateral canals formed an angle of 25º with the Read horizontal plane and is tipped with respect to the sagittal plane with higher part medially and lower part laterally. Anterior canal and lateral canal formed angle of ~93º and between anterior and posterior canal angle is ~96º and the posterior and lateral ~92º, respectively [74,75]. The orientation of vertical anterior canals with respect to the sagittal plane is less than 45º and posterior canal to sagittal plane is oriented with angle greater than 45º. The SCCs do not lie within a plane but have a variable amount of curvature with respect to a flat plan[76]. Distance between the center of the foramen magnum and the center of the horizontal canal is 42-50 mm. Circular diameter of horizontal canal is about 6.4 mm. Cross section of membranous canal is oval with a diameter of about 0.44 mm x 0.24 mm [77] and it occupies about 8% of osseous canal [78].

Cupula

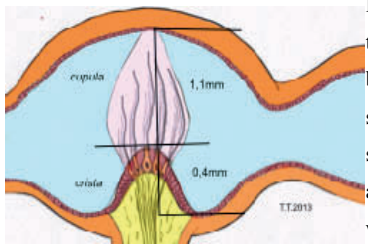


Figure 4. The ampulla of the LSCC showing the crista, hair bundles and cupula

Each of the three ampullae of the SCC has a transverse ridge, the crista ampullaris (Figure 4). Slopes of the crista are covered by sensory epithelium that consists of the sensory and supporting cells. Sensory epithelium of the lateral crista is shaped like a rectangle with rounded corners and the surface area is about 1 mm². The length extends from 1.7-2mm and the width varies between 0.6-0.8mm [79]. The height of the LSCC crista is 0.40 mm and height of the covering cupula is 1.11mm [77]. The cupula bridges the width of the ampulla, forming a fluid barrier.

Morphologically, the cupula consists of the proteoglycans secreted from the supporting cells and net-shaped tubular structures. The cupula extends from the epithelial cell surface to the roof of the ampulla and covers the neuroepithelium.

The neuroepithelium (Figure 5) contains the hair cells, an average of 7600 [79] divided into the two different types [80]. The type I hair cells are concentrated mostly in the central part of the crista and the type II cells occupied predominantly occupy the peripheral zone. A bunch of the stereocilia and one kinocilium extend from the body of the sensory cells [81]. Stereocilia are always shorter than the kinocilium, the shortest stereocilia are located more towards the peripheral and the tallest stereocilia are closer to the kinocilium.

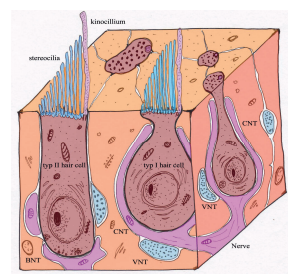


Figure 5. Cross section of vestibular neuroepithelium showing two types of hair cells

Head rotation in the plane of the semicircular canal provokes endolymphatic flow. The inertia of the endolymph produces the forces across the cupula, distending it and causing the displacement of the hair bundles and hyperpolarisation or depolarization in the hair cells within in the crista. The kinocilium is oriented towards the utriculus in the LSCC and away from the utriculus in the vertical canal. A deviation of the hair bundle towards the kinocilium is accompanied by depolarization of the sensory cell; a deviation of the hair bundle in the opposite direction is accompanied by hyperpolarization of the cell [80].

There is a lack of information about the exact topographical anatomy of the long axis of the cupula in the plane of the LSCC. Reports of the exact shape of the cupula and its orientation are scarce because of its vulnerability to chemical and fixation procedures. Observations in vivo have carried out on the lower vertebrates [82]. Judging from those studies the cupula has a cylindrical shape. The cupula sits on the crista and extends towards to the ampullary roof where it is attached. In a histological study on the crista ampullaris from 1972, Rosenhall[79] noticed that there is some kind of irregularity in shape at the inferior end of the lateral crista and at the same time it is closer to the utriculus than the superior end of the lateral crista. Takagi et al. in 1989 [83]studied the spacial relations between semicircular canals and their cristae in humans by using computer aided 3-D reconstruction. They found that the LSCC crista was not perpendicular to the horizontal plane. They also found the 65° angle between the plane of the LSCC and the long axis of the crista. Furthermore, the inferior end of the crista shifts posteriolaterally and

anteriomedially at its superior end. This finding indicates that crista is not perpendicular to the plane of the LSCC and to the Reads horizontal plane, respectively. Baloh et al. 1995 [3] suggested that the long axis of the cupula is nearly parallel to the ipsilateral PSCC. However, in a recent study, Curthoys et al. [84] demonstrated that the long axis of the crista and cupula of the LSCC is almost parallel to the median plane of the head. Bradshaw et al. in 2009 made labyrinth reconstructions from high resolution CT scans of 34 ears and found that the degree of non-planarity for the three canals varies significantly between the subjects [85]. Therefore, knowledge of the topographical properties of the cupula and semicircular canal would be indispensible in the understanding of the effects of the "heavy "and "light" cupula. Inclination of the cupula is likely to be a determinant factor in nystagmus direction in pitch plane.

Vestibulo-ocular reflex

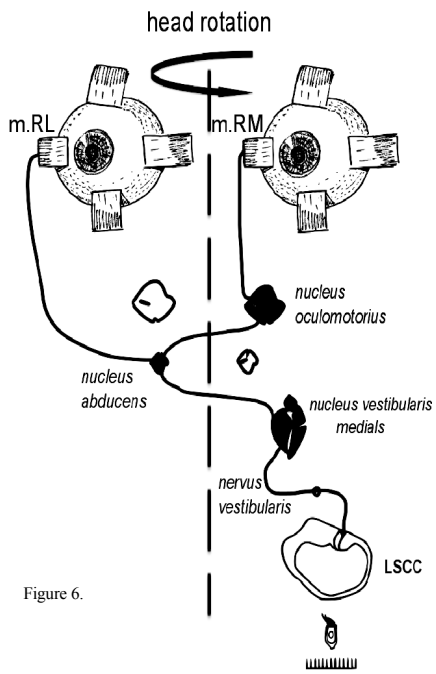


Figure 6.

During angular head movements to one side in the horizontal plane, the LSCC on this side is excited (Figure 6) and the canal on the other side is inhibited. Excitation in the LSCC is a result of cupula displacement towards the utriculus or ampullopetal cupular deviation. Inhibition in the coplanar canal is a result of cupula deviation away from the utriculus or ampullofugal cupular deviation. While the head is at rest, the primary vestibular afferents have a tonic discharge, which is exactly balanced between the corresponding canals. The SCC detects angular acceleration of the head and is responsible for the generation of the slow phase of the rotational vestibulo-ocular reflex (VOR). The VOR is optimally suited to reduce retinal image slip during high frequency head movement when visual mechanisms are insufficient for gaze stabilization. This is a three-neuron arc where the vestibular ganglion, vestibular nuclei and ocular motor nuclei are relaying the head movements into the eye movement response. For example, activity in the left LSCC excites neurons in the left vestibular nucleus relaying activity to the contralateral nucleus abducens and ipsilateral nucleus oculomotorius. The result is a contraction of the left medial and right lateral musculus recti oculi followed by a reflexive eye movement to the right. At the same time by inhibition in the ipsilateral abducens nucleus and contralateral oculomotorius nucleus the left lateral and right medial musculus recti contribute to conjugated eye movements to the right [72].

Positional Alcohol Nystagmus (PAN)

Substances such as alcohol [10,11,86], glycerol [19,67]and heavy water change specific gravity of the cupula in relation to the endolymph. Thereby this transforms the SCCs into gravity-sensitive receptors (the buoyancy hypothesis) [19].

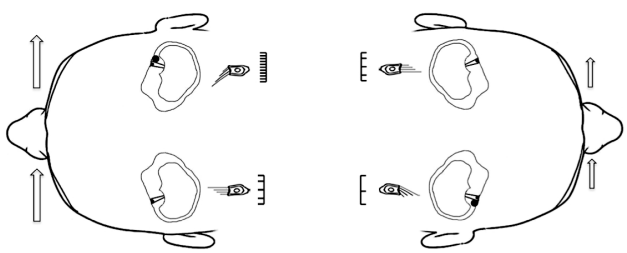
The vestibular system plays an important role in the origin of PAN [87]. It cannot be elicited in bilateral labyrinthectomized rabbits and disappears in weightlessness [13,14,88]. In the first phase of PAN the cupula becomes a gravity-sensitive receptor and causes persistent g-PDCN. The intermediate period (IP) occurs after PAN 1 under the "falling phase" of the alcohol level in the body. Under this period of time endolymph acquires the same concentration of ethanol as the cupula and nystagmus disappears. Finally, alcohol diffuses out of the cupula before it leaves the endolymph. This causes the cupula to be heavy; initiating PAN 2, which begins between 5-10 hours after cessation of drinking and is recognized by persistent a-PDCN. When a subject after ingesting alcohol lies in supine position with his head turned sideways, so that the LSCC is aligned with the true vertical, a persistent, mainly horizontally (g-PDCN) nystagmus will be elicited [18]. The nystagmus directed to the undermost ear is elicited by ampullopetal deviation of the cupula in the undermost ear and an ampullofugal deviation in the uppermost ear. However, when the cupula becomes heavy during PAN 2 the persistent nystagmus will be of opposite direction or a-PDCN [16]. When both cupulae in the LSCCs are deviated equally towards or away from the ampullae such as with head straight forward in the prone and supine positions in the pitch plane no nystagmus will be elicited. If only one cupula in the LSCC is too light or too heavy a horizontal nystagmus will be provoked in the supine and prone head positions. We have used the alcohol effect on one of LSCCs to simulate the condition of the light and heavy cupula and to analyse nystagmus directions in the pitch plane[21,22].

Concept of the heavy cupula

The condition of the heavy cupula is supposed to be caused by a dysfunction in one of the LSCC where the cupula has gained a larger specific weight than the surrounding endolymph ("cupulolithiasis"). The resulting heavy cupula makes the SCC sensitive to the linear accelerations and gravity. When a patient (Figure 7) with a heavy cupula in one of the LSCCs is lying in the supine position on the affected ear the cupula will, because of gravity, deviate ampullofugally and causes a persistent nystagmus towards the unaffected ear. Ampullopetal deviation of the affected cupula in the supine position with the affected ear uppermost causes the apogeotropic nystagmus of higher a velocity than apogeotropic nystagmus when the subject has the affected ear undermost [59,89]. This concept of different nystagmus velocity in supine side positions is based on Ewald's second law: "In the lateral canal ampullopetal endolymph current provokes a stronger reaction than the ampullofugal current."[23]. Nystagmus characteristics in heavy cupula: positional, persistent, no latency, no fatigability[5,90]. A null position for the nystagmus in the supine position could be determined when the patient`s head was slightly turned to one side[4].

In the concept of cupulolithiasis it is considered sufficient to evaluate nystagmus velocity of the apogeotropic nystagmus to determine the affected side, [91-93] but not consistently[94].

A



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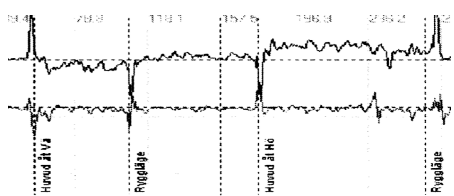
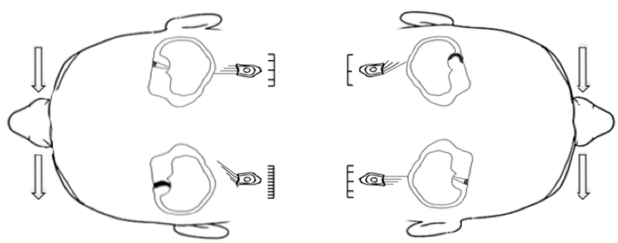


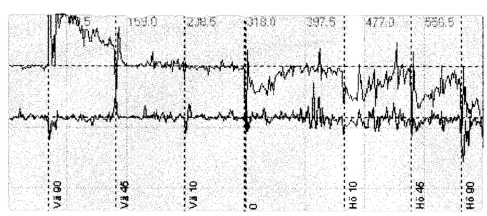
Figure 7. Cupula deviation in a patient with a heavy cupula in the right ear (A). Nystagmus recording in a patient with heavy cupula on the left side (B). The upper trace represents the SPV of horizontal nystagmus. Downwards shift of trace indicates slow phase to the left, upwards shift indicates slow phase to the right. The first section is when the patient's head was in the supine left position and nystagmus was directed to the right. In the supine position with nose up (second section) nystagmus is directed to the left. When the patient's head is turned to the right (third section) nystagmus with increased SPV is beating to the left. Nystagmus in three different head positions was recorded over circa 300 sec. The lower trace represents the SPV of vertical nystagmus.

Concept of the light cupula

Bohmer in 1990 [95] and Hiruma and Numata in 2004 [8] reported a continuous geotropic nystagmus in patients with audio-vestibular disturbances. In our Paper I from 2006, we have presented patients with vertigo and a persistent g-PDCN. The pattern of a persistent geotropic nystagmus is known from human studies after ingestion of alcohol [11,18]. This is explained by the theory that due to alcohol the cupula has become relatively lighter than the surrounding endolymph making it sensitive to the gravity[19]. Patients with light cupula in the undermost ear (Figure 8) display nystagmus directed to the affected cupula that deviates ampullopetally. When patients have the affected ear uppermost the cupula in the affected ear deviates ampullofugally that leads to nystagmus, directed to the healthy side. Theoretically the nystagmus would be of the highest intensity with the affected ear undermost. Our contribution to the concept of light cupula is quantification of the nystagmus in different head positions both in yaw and pitch plane. We have also found that nystagmus in the head forwards position was opposite to that in the head backwards position. Nystagmus characteristics in light cupula: positional, persistent, no fatigability.

A.

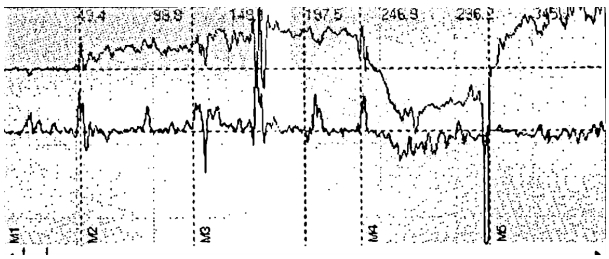




B.

Figure 8 (A, B). g-PDCN in a patient with a light cupula in the left ear (A). Nystagmus recording (B). The upper trace represents the SPV of horizontal nystagmus; the lower trace represents the SPV of vertical nystagmus. The first section in the upper trace is when patient's head was in supine left position and nystagmus was directed to the left. The zero zone is from 45° SL to 0° (section 2 and 3). The patient's head in the supine position (section 4) provoked right beating nystagmus, which is of peak velocity when the patient's head gradually (section 5 and 6) was turned maximally to the right (section7). Nystagmus in different head positions was recorded over circa 600 sec.

C.



D.

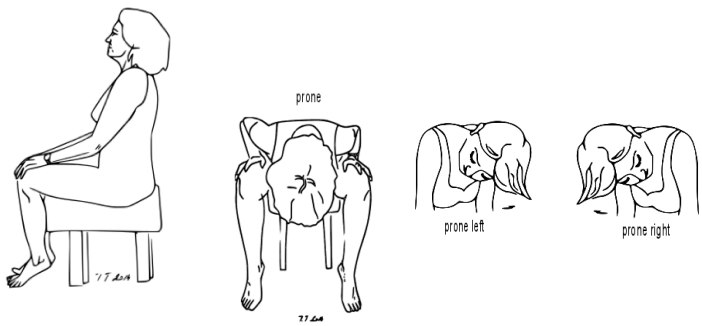


Figure 8. Nystagmus recording (C). The upper trace represents the SPV of horizontal nystagmus; the lower trace represents the SPV of vertical nystagmus. The first section (M1) of the upper trace is when patient's head is in upright position, in section M2 the head is bend forward and maximally forward in M3. In both sections nystagmus is directed to the left. The fourth section (M4) is when patient's head is bend forward and turned to the left and nystagmus is beating to the right. The fifth section is when patients head is bend forward and turned to the right and nystagmus is beating to the left. Illustration for head positions in D.

AIMS OF THE THESIS

This study was performed:

I. To record and describe nystagmus characteristics in different head positions in the patients with a persistent g-PDCN
II. To analyse nystagmus directions in different head positions in experimental conditions on hemi-labyrinthectomized subjects.
III. To correlate nystagmus findings in experimental studies with nystagmus findings in patients with positional nystagmus of both geotropic and apogeotropic types.
IV. To analyse nystagmus in different head positions and correlate it to the results of the vestibular tests in an extended patient study of those that have g-PDCN.
V. To find a clinical pattern in nystagmus direction to determine the affected side.
VI. To discuss the possible pathophysiological mechanism behind this condition.

MATERIALS AND METHODS

Study populations

Paper I

In this case report we assessed six patients with g-PDCN selected from our tertiary clinic. Patients were selected because they displayed g-PDCN during the acute onset of vertigo. None of the patients were on drugs known to cause vestibular symptoms or nystagmus and none of the patients consumed alcohol at least 24 h before examination.

Papers II and III

This experimental interventional study was conducted on eight subjects divided into two groups.
The control (bilateral) group comprised three healthy subjects.
The experimental (unilateral) group consisted of five subjects. Subjects 1 and 2 had been labyrinthectomized on the left side 6, and 8 years earlier. Subjects 3 and 4 had been labyrinthectomized on the right side 9 and 6 years earlier. Subject 5 had unilateral loss of right inner ear function after gentamicin treatment for Meniere's disease 15 years earlier. All subjects were free from attacks of vertigo.

Paper IV

In this study we assessed 20 patients, 7 men and 13 women with mean age of 53 years (21-83), with g-PDCN. They were recruited at our tertiary clinic during acute onset of vertigo and position induced horizontal nystagmus within the last 48 hours. They were followed until 2011 when the study was completed.
Criteria for inclusion for patients entering the study:

- Nystagmus was recorded and quantified by the slow phase velocity (SPV).
- Velocity of g-PDCN should be at least 1°/s with a duration exceeding 60 s.
- Vestibular laboratory tests should have been performed within 2 days from registration of g-PDCN.
- No alcohol should have been consumed during the last 24 hours and the patients should be free from drugs that possibly could elicit vestibular disability and nystagmus.
- There was no effect on nystagmus characteristics after liberatory maneuvers.
- All patients should be free from oculomotor disturbances, clinical and Magnet Resonance Imaging signs of Central Nervous System engagement.

At the end of the study in 2011, at follow up (FU), patients included in this study underwent a final examination to assess the following parameters:

- Frequency and duration of vertigo (the sensation of spinning or moving around) during the past 12 months.
- Recording and quantification of nystagmus in different head positions.
- Examinations using the caloric test, subjective visual horizontal (SVH), cervical vestibular evoked myogenic potential (c-VEMP), and ocular vestibular evoked myogenic potential (o-VEMP).

Ethical permission

All the subjects gave informal consent to participate. The local ethics committee approved all four studies.

Methods

Qualitative and quantitative analysis of nystagmus

In all four Papers, video-nystagmoscopy was used for visualization of eye movements and graphical recording of nystagmus. The peak velocity of the positional, spontaneous and post-caloric nystagmus is considered representative for each patient and it was quantified by the slow phase velocity (SPV) in °/s. After a slow head turn, nystagmus was recorded in each position for 60 s. Recording started 5 s after head movement stopped.

In the different positions, pathological nystagmus was considered to be present when five or more consecutive nystagmus beats were identified [96].

Spontaneous nystagmus was defined as nystagmus occurring when the head was kept upright and straightforward in a position normal for the test subject. In all four studies both subjects and patients are submitted to analysis of nystagmus characteristics in different head positions and zero zone.

Head positions

1. supine (head elevated 30°, LSCC vertical), S;
2. supine left (head turned to the left 90°), SL;
3. supine right (head turned to the right 90°), SR;
4. upright (sitting, head in normal position and straight forward), U;
5. prone (torso and head bent forward, LSCC vertical), P;
6. prone left (head turned to the left 90°), PL;
7. prone right (head turned to the right 90°), PR.

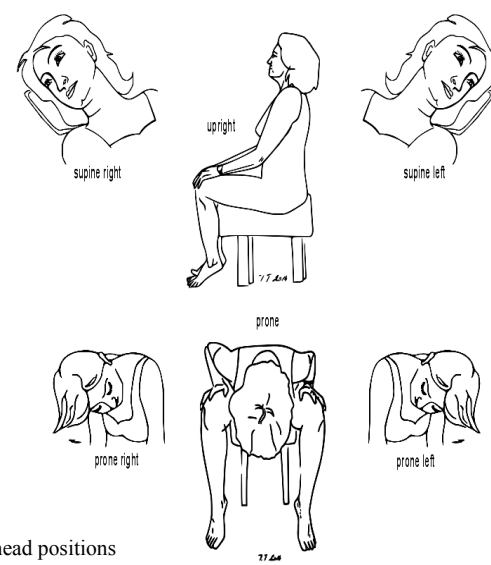


Figure 9. Illustration of different head positions

In Papers I and IV patients were submitted to the first five of the head positions as described above (without pronation left (PL) and pronation right (PR)). In Paper IV nystagmus was only recorded for direction in the prone position. In Papers II and III all eight subjects were submitted three times to all seven head positions: before alcohol ingestion, during PAN 1 and PAN 2.

Zero zone

The zero zone was determined by slowly rotating the subject's head in the supine position from left ear down to right ear down, a zone was sought where there was no nystagmus and beyond which the nystagmus changed direction.

Vestibular tests

The subjects in studies II and III were examined with vestibular tests one day before experiments to evaluate the vestibular function on both sides in the bilateral group and on the healthy side in the unilateral group. One of the labyrinthectomized subjects did not allow caloric testing. However, the response to the head impulse test directed toward the labyrinthectomized ear was absent and without notice to the healthy ear. The subject who had undergone unilateral gentamicin treatment was tested with bilateral caloric irrigation. No nystagmus was elicited on the gentamicin-treated ear, neither with warm water in the supine position or with ice water in the prone position. An absence of response was demonstrated with c-VEMP. The c-VEMP test was normal on the healthy side in all of the subjects.

Patients in study IV during onset and follow up were submitted to the caloric test, subjective visual horizontal (SVH) and cervical vestibular evoked myogenic potential (c-VEMP) at onset and at FU. In the same study patients we submitted to o-VEMP at FU. All vestibular tests were performed according to standardized procedures at our Department [97].

Caloric Test

Bilateral bithermal caloric stimulation was used.

The nystagmus was quantified by the SPV. The peak velocity of the post-caloric nystagmus after four water irrigations is considered as caloric response. The caloric side difference was calculated according to the Jongkees and Philipszoon formula[98].

A Caloric Ratio (CR) $\geq$ 0, 2 (20% difference) was considered pathological[99].

SVH

The subjective visual horizontal (SVH) is a measure of spatial orientation in the roll plane. A component in the spatial orientation is the ability to perceive the direction of gravity and therefore dependent on the input from the vestibular receptors. This ability can be tested quantitatively by asking the subject to align a dimly illuminated light bar with the gravitational horizontal in a completely darkened room. Both the SVH tilt (deviation from the true horizontal) in the upright position and the asymmetry in tilt perception, have been suggested to reflect the asymmetries in the morphology and function of the utriculus. Test procedure and the limits of pathology have been described earlier [100]. In our present Paper we choose to show SVH test results taking into consideration if the results were pathological or not.

c-VEMP

Cervical VEMP are loud clicks that evoke ipsilateral relaxation of a tonically contracted sternocleidomastoid muscle. The response is considered to be of saccular origin. Asymmetry in the click induced VEMP was considered pathological at a 40% difference in corrected amplitudes [101].

o-VEMP

At the FU the patients were also submitted to recordings of ocular evoked myogenic potentials, o-VEMP was standardized at our department in 2010[102]. The stimulus for ocular VEMP was air-conducted 500 Hz tone burst. O-VEMP consists of a negative/ positive deflection corresponding to a short latency activation of the inferior oblique muscle of the contralateral eye. The response is considered to be mainly utriclar. Asymmetry of 40% in amplitude is considered pathological.

Alcohol dosage and procedures for measuring blood alcohol levels

To elicit PAN in studies II and III, all participants drank 0.68 g ethanol (95%) per kg body weight, diluted about 1:3 in a soft drink, consumed within 30 min as suggested by Jones et al.[103]. The presence of ethanol on the breath was measured by an alcohol analyzer (Safeway, Paramint AB, Uppsala, Sweden) with a detection range from 0.1‰ to 1.0‰, before ingestion and every 20 min, then again 20 min after the breath level had reached 0‰. During PAN 1, blood alcohol concentration was also determined in mM with a sample taken from the cubital vein (on average, 68 min after the last alcohol intake). The blood alcohol level expressed in mM was recalculated in pro mille as suggested by the Lund Forensic Institute (personal correspondence) (1 mM ethanol in blood = 0.038 ‰ breath ethanol). A zero alcohol breath level was present 4–5 h after alcohol intake (14–17 measurements). PAN 2 started about 6–7 h after alcohol intake ceased.

Questions about the frequency and duration of vertigo

In study IV at FU patients reported about the frequency and duration of vertigo (the sensation that the things are spinning or moving around) in the past 12 months. This question is extracted from a questionnaire (Vertigo Symptom Scale) VSS which has been validated and designed by Yardley [104]. Scores are ranged from 0 to 4. The frequency of the symptom is rated on a 5-points scale: 0 points: “never”, 1 point: “a few times (1–3 times a year)”, 2 points: “several times (4–12 times a year)”, 3 points: “quite often (more than once a month)” and 4 points: “very often (more than once a week)”. Duration is rated: >2 min, >1 hour, <1hour, whole day. Each patient had the possibility to choose more than one combination, with the aim being to achieve better descriptions of the specific vertigo type.

Statistical method

Papers II and III

Nystagmus SPV for different head positions was presented as mean. Analysis of variance was used for statistical treatment of data. Statistically significant difference was considered at $p < 0.05$.

Paper IV

All data were presented using descriptive statistics, mean, standard deviation, median, minimum, maximum for continuous variables and frequency for categorical variables. In the analysis of the continuous variables we used a non-parametric approach. To compare independent groups, the Mann-Whitney U test was used. To assess the significance of the difference between two correlated proportions McNemar's test was used. Correlation was estimated using the Spearman rank order correlation coefficient. We use the Fisher exact probability test to calculate differences between independent groups.
All tests were two-sided and $p< 0.05$ was regarded as statistically significant.

RESULTS

Paper I

In this case report none of the six patients revealed affection of the CNS during neurological examination. Two patients with vestibular dysfunction had associate auditory symptoms on the same side. In both patients nystagmus in the prone position was directed to the non-affected side and in the supine position nystagmus was directed to the affected side.
The other four patients with g-PDCN were without lateralizing symptoms. We applied the results of nystagmus direction in different head positions from the previous two patients to estimate the affected side. The combined nystagmus pattern with respect to the direction of nystagmus in the pitch plane and the zero zone indicated the affected side as shown in Table 1. However the prerequisite was that the long axis of the cupula is aligned with the ipsilateral anterior SCC.

Position	Patient											
	1		2		3		4		5		6	
Nose down (prone)	←	-	←	8°/s	→	3°/s	←	2°/s	→	5°/s	←	6°/s
Supine	→	-	→	7°/s	←	3°/s	→	2°/s	←	1°/s	→	4°/s
Supine left	→	4°/s	→	21°/s	→	12°/s	→	9°/s	→	6°/s	→	25°/s
Supine right	←	9°/s	←	7°/s	←	12°/s	←	6°/s	←	4°/s	←	24°/s
Zero zone	-		-		20°L		10°R		20°L		30°R	
Affected side	Left		Left		Right?		Left?		Right?		Left?	

Table 1. Nystagmus direction and SPV in 5 different head positions and zero zone in six patients with g-PDCN.

Paper II

Alcohol level

The blood alcohol level ranged between 18 mM and 29 mM for both groups and the concentrations are considered sufficient to elicit PAN1[15].

Nystagmus findings

Bilateral (control) group

All three subjects had no nystagmus during the series of head positions before alcohol intake. During PAN1 all subjects displayed g-PDCN in lateral head positions both in the yaw (SR and SL) and pitch (PL and PR) planes. We found no difference in SPV for nystagmus directed toward the right or the left for positions SL and PR taken together, as opposed to positions SR and PL taken together. No nystagmus was found in the pitch plane represented by P, U and S positions except in the prone position in one subject.

Unilateral (hemi-labyrinthectomized) group

In the unilateral group all subjects demonstrated nystagmus (1-4°/s) in two or more of the various head positions before alcohol intake. For position U that also represents spontaneous nystagmus 4/5 subjects demonstrated nystagmus directed toward the healthy ear.
After alcohol intake (Table 2) all subjects were recorded with g-PDCN in both the yaw and pitch planes. To evaluate the real effect of alcohol we have corrected results of nystagmus after alcohol intake for direction and SPV with the corresponding values before alcohol intake. These corrected results are then arranged taking direction and velocity into consideration; if it is beating to the labyrinthectomized ear or away from it.

Position	1L	2L	3L	4L	5L
SL	→ 9	→ 8	→10	→ 7	→ 8
SR	← 4	← 4	← 5	← 6	← 4
PL	← 5	← 3	← 4	← 1	← 3
PR	→ 4	→ 6	→ 2	→11	→20

Table 2. Nystagmus direction and SPV during PAN 2 corrected for before alcohol intake. The five unilateral subjects were examined with the head turned to the left and right in the supine (SL, SR) and prone (PL, PR) positions. For statistical comparison, two first subjects, left-sided labyrinthectomies were converted to right-sided. L in subjects 1L–5L denotes tested left ear. ←Indicates nystagmus direction of fast phase to the right.

The mean value for nystagmus directed toward the non-labyrinthectomized ear (affected with alcohol) was 8.5°/s, for positions SL+PR, which was significantly higher than the corresponding value, 3.9°/s, for positions SR+PL for nystagmus toward the labyrinthectomized ear ($p = 0.048$).
We also found that the mean value for nystagmus SPV for SR, SL, PL and PR was lower in the unilateral group than the corresponding value for the bilateral group. The pitch plane nystagmus, represented with direction and SPV in the supine and prone positions was corrected for nystagmus direction and SPV before alcohol intake (Table 3). In S and U, all but one subject (4R) displayed nystagmus directed to the labyrinthectomized ear. In the prone position nystagmus was directed in all subjects toward the non-labyrinthectomized ear. However, there was no significant difference in SPV between nystagmus in positions S, U and P.

Position	1L	2L	3L	4L	5L
S	← 2	← 2	← 1	→ 1	← 6
U	← 2	← 2	← 1	0	← 2
P	→ 2	→ 2	→ 3	→ 7	→ 7

Table 3. The five unilateral subjects have different nystagmus directions in pitch plane. For statistical comparison, left-sided labyrinthectomies were converted to right-sided. L in subjects 1L–5L denotes tested left ear. ←Indicates nystagmus direction of fast phase to the right.

Zero zone

After the direction and SPV of nystagmus were corrected for before-alcohol intake, we found that in 4/5 subjects the nystagmus reversal occurred when the head was turned to the side *affected* with alcohol.

Paper III

Alcohol level

PAN 2 started about 6–7 h after alcohol intake. Zero alcohol level was measured by a breathalyser 4- 5 hours after alcohol consumption terminated.

Nystagmus findings

Bilateral (control) group

Before alcohol intake, none of the bilateral subjects had any spontaneous or position- induced nystagmus. During PAN2 all subjects displayed an apogeotropic nystagmus in positions: SL, SR, PL and PR, mean SPV was 4.58°/s. No nystagmus preponderance was found between right beating nystagmus in position SL+PR, as opposed to a left-beating nystagmus in positions SR+PL. No nystagmus was found in the supine position. In the prone position two of the subjects showed left beating (1°/s) nystagmus.

Unilateral (hemi-labyrinthectomized) group

In the unilateral group all subjects demonstrated nystagmus (1-4°/s) in two or more of the various head positions before alcohol intake as reported in Paper II. All subjects displayed nystagmus during PAN 2 of apogeotropic direction in both the supine and prone lateral head positions: SL, SR, PL and PR, except for subject 4L when in position SL (Table 4).

Position	1L	2L	3L	4L	5L
SL	← 4	← 4	← 2	nc	← 5
SR	→ 7	→ 2	→ 2	→ 2	→ 1
PL	→ 5	→ 1	→ 1	→ 3	nc
PR	← 7	← 4	← 4	← 2	← 2

Table 4. Nystagmus direction and SPV during PAN 2 corrected for before alcohol intake. The five unilateral subjects were examined with head turned to the left and right in the supine (SL, SR) and prone (PL, PR) positions. For statistical comparison, left-sided labyrinthectomies were converted to right sided. L in subjects 1L- 5L denotes tested left ear. ← indicates nystagmus direction of fast phase to the right. "nc"; no change in nystagmus direction or velocity compared to before alcohol intake.

The results for nystagmus direction and SPV were corrected for the baseline value recorded before alcohol intake. But to have a better overview of the effects of alcohol on nystagmus direction we have organized and unified the data considering which side has been labyrinthectomized or not.

The two left sided labyrinthectomized subjects with nystagmus SPV and direction were transformed into right-sided subjects and they were denoted as being affected on the left (L) side with alcohol. The mean value for nystagmus velocity towards the labyrinthectomized ear was significantly no different than the corresponding value for nystagmus towards the non-labyrinthectomized ear. Mean velocity for ampullofugal deviation of the cupula was 3.4°/s and for ampullopetal deviation of the cupula 2.4°/s. Difference in SPV of the apogeotropic nystagmus in the four positions (SL, SR, PL and PR) between the bilateral and unilateral groups was not significant. In the supine position the nystagmus was directed towards the ear affected with alcohol in three of the subjects. In the prone position, all subjects demonstrated nystagmus directed to the labyrinthectomized ear (Table 5).

Position	1L	2L	3L	4L	5L
S	→ 1	nc	→ 5	→ 1	← 1
U	← 3	nc	← 6	→ 2	← 1
P	← 4	← 1	← 2	← 1	← 1

Table 5. The five unilateral subjects have different nystagmus direction in pitch plane. For statistical comparison, left-sided labyrinthectomies were converted to right-sided. L in subjects 1L–5L denotes tested left ear. ←Indicates nystagmus direction of fast phase to the right. nc, no change in nystagmus direction or velocity compared to before alcohol intake. (0), no nystagmus found.

Zero zone

In subjects 1, 2, 3, and 5, the zero zones were recorded when the head was turned to the side of the affected ear. In subject 4L, no nystagmus was present in the left lateral position, but a left beating nystagmus commenced when the inclination of the head was 10° to the left of the midline, and persisted throughout the whole tested sequence.

Paper IV

Twenty patients with g-PDCN were included in the study. Among them, the incidence of lateralizing auditory symptoms as an indication of the affected side, occurring together with the onset of vestibular symptoms were rare. Seven patients had previous history of benign paroxysmal positional vertigo of the posterior canal and eight had a medical history of migraine classified according to the second edition of the International Headache Classification (ICHD-2) criteria. In three of these patients, the incidence of g-PDCN was associated with a migraine attack.

Onset

The median SPV for left beating nystagmus was 5,5°/s and 3,5°/s for right beating nystagmus (p=0,707). For the 18 patients who demonstrated nystagmus in S position, the zero zone was localised on the opposite side. In 72% of the patients, horizontal nystagmus was of opposite in directions while in the P compared to S position. Spontaneous nystagmus was recorded in 45% of the patients with nystagmus SPV ≤ 5°/s.

To examine whether a deviation from the resting position of the cupula (i.e., the discrepancy between the densities of the endolymph and cupula) expressed as nystagmus in the S position was related to the difference in g-PDCN (GSD), we analysed the correlation between velocity of the nystagmus during S position and GSD and found a significant correlation (Figure 10; $p < 0.05$, $r_s = 0{,}634$) . Hence, the higher nystagmus velocity in the S position, the higher the difference in velocity of the geotropic nystagmus (Figure 10).

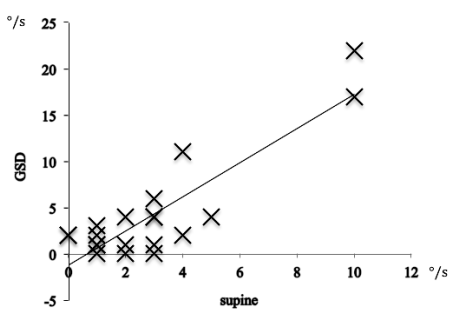


Figure 10. There is a linear correlation between nystagmus velocity in supine position and a difference in velocity of the geotropic nystagmus (GSD).

In 65% of patients CR was pathological. In seven subjects, the pathologically reduced caloric reaction was on the right side and in six subjects on the left side. To examine whether the side difference in SPV between geotropic nystagmus directed to left or right (GSD) could serve as an indicator of the affected side, we analysed the caloric test results as a reference of the pathologic side in relation to GSD. For the group as a whole, there was no correlation ($r_s = -0.0697$, $p = 0.768$). However, for three patients with a GSD >10°/s, the CR showed pathology on the side with a greater SPV .

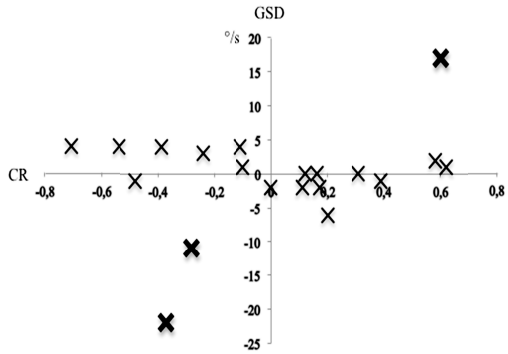


Figure 11. The individual geotropic side difference values (right beating nystagmus – left beating nystagmus = GSD) in correlation to the caloric ratio (CR) for the 20 patients. CR ≥ 0.2 is considered pathological. The pathological side was the same only in three subjects with GSD >10°/s and CR ≥ 0.2 . The positive value depicts the left side and a negative value depicts the right side.

In theory, in cases of light cupula, the nystagmus in the S position should be directed to the non-affected side. If, as here, the caloric side difference is regarded as the pathologic side, the nystagmus in the S position should be directed opposite to the side with caloric impairment. Among our 13 patients with a CR ≥ 0.20, there was no significant correlation between the side with an impaired caloric response and the direction of nystagmus in the S position (rs = -0.102, p = 0.740) (Figure11).

Of 17 patients subjected to SVH analysis 59% showed pathological result. Of the 13 patients we tested for c-VEMP, only two showed pathological results. A combination of pathologic CR, SVH, and cVEMP on the same side occurred in only one patient with sudden deafness on the same side as the pathologic test results. Eight (40%) of the 20 patients with g-PDCN had a medical history of migraine (in accordance with ICHD-2), of which 65% were female. Statistical analysis showed no significant difference in any variable between patients with migraine and patients without migraine. There was no difference in the sum of the four caloric nystagmus reactions (SPV) between the two groups; however, among the patients with a history of migraine, the sum of caloric reactions was 50°/s or more.

Follow-up

At the end of the study in 2011, all 20 patients who met the inclusion criteria and participated in the study from its onset were invited by mail or phone to undergo a follow-up examination, of whom 18 (80%) replied positively. However, six patients found the earlier vestibular tests unpleasant and refused further testing and two recovered sufficiently and had no desire to participate in extensive vestibular testing. Therefore, a total of 10 patients (7 women and 3 men; mean age, 60 years) finally consented to further neuro-otological examinations using the vestibular tests (caloric test, SVH vestibular function, c-VEMP and o-VEMP) in 2011. Time for FU ranged between 1 and 7 years.

At FU, four patients demonstrated g-PDCN and one presented with a-PDCN. In four patients nystagmus was recorded in the S and P positions, but only one exhibited a change in nystagmus direction from the S to P position.

The median value for nystagmus in S for the same patients significantly decreased in FU. Spontaneous nystagmus was disappeared. For 10 patients, there was no significant difference between CR at onset and FU (p > 0.50)

SVH test was assessed in all 10 patients, of whom 5 (50%) demonstrated pathological results. At FU, 2 of

the 10 patients showed pathological results in c-VEMP; however, none of these patients showed pathological c-VEMP results at onset.

Vertigo during the last 12 months was self-reported by 14 (78%) out of 18 patients. About 60% of the patients have shorter attacks. Of them about 20 % have attacks more that one time per week and additionally 20 % have attacks 1-3 times per year. Remaining 20 % could have short vertigo disability from 4 times per year to more than 1 time in month. Characteristics for vertigo attacks shorter than 1 hour is that 40 % of the patients had reported different frequency from more than once in month to three times per year. Patients that reported vertigo symptom during whole day (40%) in the majority about 30%, had problem from 1-3 times per year. Figure 12 below presents more information about different types of duration and frequency of vertigo.

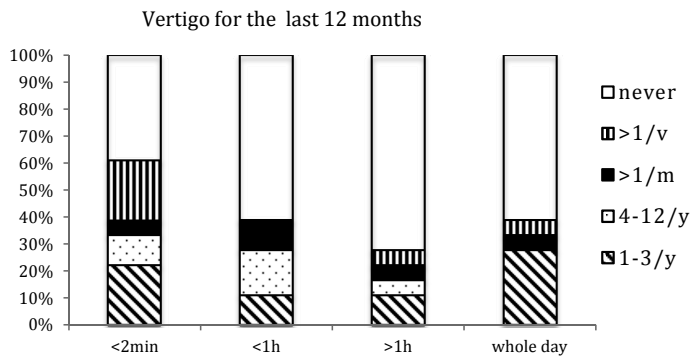


Figure 12. Vertigo attacks with respect to duration and frequency expressed in percentage of the 18 patients.

DISSCUSSION

Methodological consideration

Paper II and Paper III are based on the experimental study with alcohol. Statistical analysis for the unilateral group have shown power ranged from 5-20. We chose to show power figures in Paper III to acknowledge the limited sample size

- We had difficulties to recruit unilaterally labyrinthectomized subjects
- Study was time consuming both for subjects and for staff members at the Department. Only recording of nystagmus in seven different head positions have been done at least three times
- All vestibular tests should be done the day before experiments
- Subjects would drink alcohol to the level of intoxication

We had three subjects in the control group; with the third subject we achieved good nystagmus reproducibility. We considered it sufficient.

Paper IV

Considering the large number of patients investigated at out tertiary clinic during the period of clinical study with patients with g-PDCN (2004-2011) the population of 20 patients is surprisingly small. This is explained mainly by the fact that this type of dizziness is not recognized with its own characteristic and is classified by other specialists at a primary level, probably into other diagnoses i.e., mostly BPPV. Quantification of nystagmus and vestibular tests were performed by regular staff members and coordinated by one researcher (T.T.)

The vestibular test was not available for all consecutive patients with g-PDCN because of organizational difficulties. Vestibular laboratory at the Department of Hearing and Neurotological Disorders had appointments for elected clinical activities and to arrange the acute appointment for vestibular tests battery required extraordinary effort from staff members.

There are other factors that made it difficult to recruit patients.

- Recurrence of positional vertigo and anxiety connected to the positional and vestibular tests that could provoke vertigo attack or make it more severe.
- Patients felt a certain level of frustration suffering from unknown kind of vestibular disturbance, which may also be resistant to the repositioning procedure, and the choice of medication is limited.
- Examination is time consuming

About 50% of the patients from onset consented to further neurotological examinations using the vestibular tests. Dropouts found the earlier vestibular tests unpleasant and refused further testing or some of them recovered sufficiently and had no desire to participate in extensive vestibular testing.

Nystagmus in lateral head positions – summary

In Paper I, out of the 6 patients, the median SPV for left beating nystagmus was 10.5°/s and for right beating nystagmus was 8°/s (p= 0.1).

In Paper IV, out of the 20 patients, the median SPV for left beating geotropic nystagmus was 5.5°/s and 3.5°/s for right beating nystagmus (p = 0.775).

In Paper II, geotropic positional nystagmus during PAN 1 was found in both the bilateral and unilateral subjects. In positions SL and SR, all subjects demonstrated geotropic nystagmus.

The bilateral subjects' median SPV was 14°/s for left beating nystagmus and 12°/s for right beating nystagmus. In the unilateral group we found that the mean value for nystagmus directed toward the non-labyrinthectomized ear was 8.5°/s, which was significantly higher than the corresponding value, 3.9°/s, for nystagmus toward the labyrinthectomized ear (p = 0.048).

In Paper III, we used the same method to analyse nystagmus SPV and direction during PAN 2 and found significant lower nystagmus velocity then during PAN 1. The bilateral subjects' median SPV was 3°/s for right beating nystagmus and 5°/s for left beating nystagmus.

Furthermore, the mean value for nystagmus caused by ampullofugal deviation of the cupula in the alcohol affected ear in the unilateral group was 3.4°/s. Nystagmus caused by ampullopetal deviation of the affected cupula was 2.4°/s. We found nystagmus of equal velocity when the head was positioned to right and left in supine position. This finding is in line with a clinical study on 18 patients by Ichijo [105].

In Paper IV was found a close correlation between the intensity of nystagmus in supine position and GSD. The intensity of nystagmus in S may reflect a deviation from the resting position of the cupula; i.e., the magnitude of difference between the density of the endolymph and that of the cupula. This difference has an impact on the magnitude of deviation of the cupula. When the cupula is greater influenced by gravity, such as what occurs when the head is in a lateral position, the GSD increased. Consequently, the lighter the cupula becomes, the more it deviates in lateral positions and the larger the difference becomes between ampullofugal and ampullopetal deviation, as quantified by SPV.

It can be argued that in some of patients described in Paper IV, the SPV of the geotropic nystagmus was low and could be within normal physiological ranges. However, based on our normal material a position induced horizontal nystagmus was not found in any of the healthy subjects [96].

Lateralization of affected side by Ewald's second law

Ewald's second law states that ampullopetal stimulation is stronger than ampullofugal stimulation in LSCC. The affected ear can be determined during supine lateral position by the side showing more intense nystagmus in the canalolithiasis paroxysmal type and the side showing less intense nystagmus in the cupulolithiasis type [9,93,105-108]. Implementation of Ewald's second law in determination of the affected side has been used even in studies on patients with persistent g-PDCN [105]. However, experimental data from animal studies raised question about the validity of Ewald's second law on human labyrinth [109].

In clinical studies, Baloh et al. demonstrated that patients with total unilateral canal paresis show ampullopetal-ampullofugal asymmetry only at horizontal head accelerations causing nystagmus of at least 60°/s in SPV. These experimental findings provided a possible explanation of discrepancies associated with Ewald's second law. Nystagmus response induced by stimuli of a small magnitude would be roughly symmetrical as opposed to stimuli of a larger magnitude that would bring about asymmetric vestibular nerve responses [110].

Due to the small SPV found in our subjects, it is reasonable to assume that the degree of cupula deviation is too small to permit an assessment of affected side by applying Ewald's second law.

It can be argued that Ewald's second law is only valid for impulse stimuli of the LSCC leading to a transitory deviation of the cupula and not a persistent deviation of the cupula (mimicking a constant acceleration), as would be the case in patients with persistent positional nystagmus.

Maybe it is possible to induce Ewald's second law for nystagmus with lower velocity but this can be an aim for future studies. Two of our findings are worth consideration. Speaking for that the law is valid for small deviations of the cupula is the observation of the significant preponderance for ampullopetal versus ampullofugal nystagmus of low SPV as shown in Paper II. However secondly, contradicting Ewald's second law, is our observation in Paper IV where pathologic CR, defined as the affected side, does not correlate with GSD but only in the three cases with GSD > 10°/s.

Topographical orientation of the cupula- clinical implications

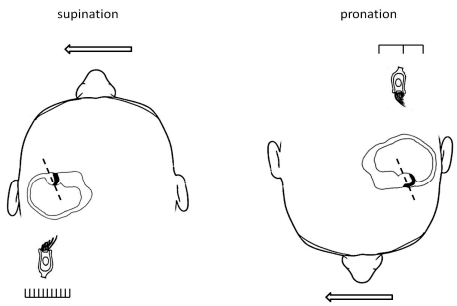


Figure 13. Light cupula in the left LSCC with its topographical orientation parallel to the ipsilateral anterior SCC. In this case nystagmus in the supine position will be directed to affected and in the prone position to the unaffected ear.

In Paper I, results from nystagmus direction in different head positions indicated a pattern for assessment of the affected side based on the buoyancy hypothesis. This is when the affected cupula in the LSCC becomes sensitive to gravity. The occurrence of a zero zone in the supine position suggests unilateral cupula dysfunction. When the head of the patient, as illustrated in the Figured 13, is positioned so that the plane of the LSCC (dashed line) is earth-vertical and the head is turned so that the affected cupula is aligned with the gravitational vertical, the cupula is in a neutral position and no nystagmus is elicited. The nystagmus findings in both the prone and supine head positions in the pitch plane were found in all four patients further strengthening the argument that the cupula is influenced by gravity. In Paper I we argued that the long axis of the cupula is approximately parallel to the anterior SCC of the ipsilateral ear (Figure 13). Anatomical studies of the SCC have shown the presence of natural variability of nonplanarity and plane orientation of the canals within the population. Theoretically, the exact anatomical arrangement may be revealed when the function in one SCC is impaired [85].

The implication of the cupula orientation is further developed in Paper II analysing the results of the study on unilaterally labyrinthectomized subjects during PAN1.

In the unilateral subjects in Paper II, the zero zone was not as well demarcated, but the change in nystagmus direction occurred when the subject's head was turned to the side of the *affected cupula.* Hence, the nystagmus pattern with the head straightforward in the prone and supine positions, as well as the side of the zero zone, is the opposite to that we have reported in patients with a light cupula in Paper I. However, if the long axis of the cupula is parallel to the ipsilateral posterior SCC (Figure 14), deviation of the cupula in the prone and supine positions of the head would be quite the opposite and in-line with the results of the study on unilateral subjects with light cupula in the functional ear. Furthermore we observed that in the upright position, four of the unilateral subjects displayed nystagmus directed toward the labyrinthectomized ear, possibly a sign of a slight ampullofugal

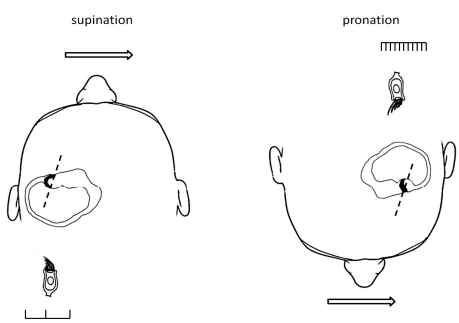


Figure 14. Light cupula in the left LSCC is in its topographical orientation parallel to the posterior SCC. In this case nystagmus in the supine position will be directed to unaffected ear and in the prone position to the affected ear

deviation of the cupula as in this position the plane of the LSCC is not aligned with the earth's horizontal plane.

Orientating the cupula axis parallel to the ipsilateral posterior SCC would also fit the localization of a zero zone, which is reached when the head is slightly rotated to the side with the light cupula. In this position the longitudinal axis of the cupula is aligned with the gravitational vertical, and no nystagmus is elicited. In this position the cupula is in its resting position, whether it is of higher or lower density than the surrounding endolymph. This is exactly what we have found in the study on the same unilateral labyrinthectomized subjects during the second phase of PAN when nystagmus is of apogeotropic direction. In all subjects, the zero zone was recorded when the head of the subject was turned towards the side with the *affected cupula.* From the results in Papers II and III it could be deduced that the long cupula axis is anteriomedially– posteriolaterally orientated in the Reid's horizontal plane.

In Paper IV we examined the nystagmus pattern in different head positions of 20 patients to compare the experimental results from the study (Paper II) with alcohol on unilateral subjects. In the search for objective signs that might indicate the affected side we referred to the caloric test results. If, as was the case here, the side with caloric impairment is regarded as the pathologic side, the nystagmus in the S position should be directed to the opposite side. However in the present study we found no correlation between S and CR, which is illustrated in Figure 15.

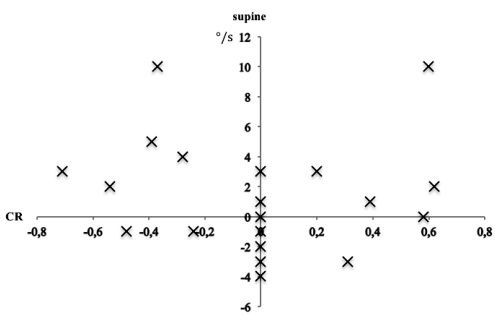


Figure 15. Relation between nystagmus in supine position and CR. Theoretically, nystagmus in S position should be directed contra-laterally to the side with caloric impairment this was met in 7/20 patients. Sex patients have nystagmus directed towards the side with impaired caloric response. (Positive values indicate impaired caloric response on the left side and nystagmus (SPV) directed to the left.

The lack of conformity in study IV between the sides of vestibular impairment quantified with CR and the direction of nystagmus in supination and the side with the most intense geotropic nystagmus respectively could, also here, hypothetically be explained by the topographical orientation of the long axis of the cupula.

It is possible that deviation in either direction from the median line, i.e., slightly parallel to the ipsilateral anterior SCC or to the ipsilateral posterior SCC, could be within normal anatomic variations.

Pathological processes, such as increased fluid volume within the endolymphatic system [111], which may have been a factor in our patient cohort, could alter the orientation of the cupula axis and shift the orientation of the axis from the median line to slightly parallel to the ipsilateral anterior SCC or to ipsilateral posterior SCC. Based on this rationale, the nystagmus direction during the S or P position is not a reliable indication as to the side with the light cupula.

Further comments on cupula dysfunctions as sign of vestibular lesion

The normal cupula adheres to the ampullary wall and separates the ampullary space. The cupula deviates according to the endolymphatic flow caused by head rotation shown in Figure 6. Maximally displacement of the cupula occurs in the central region. Calculation indicates that maximal head self-induced motion should produce the cupula motion of the midpoint of 3μm (dynamic range for cupula motion is 10 nm to 3 μm)[82]. Cupula play a decisive roll as the connecting link between endolymphatic flow and hair cell stimulation. Altered cupula mechanics may play important roll in clarifying the idiopathic vestibular disorders. An experimental study on pigeon [112] has shown that mechanical detachment of the cupula from the wall leads to vestibular disability.

Suzuki et al performed the experimental lesional studies on cupula of bullfrog [113]. He had noticed various changes of the cupula morphology, including shrinkage, deformity, and volume enlargement. The different level of morphological changes in the cupula was compared with the ampullary nerve action potential. Even when the cupula is severely damaged the physiological activity of the sensory epithelia is maintained [114,115]. They assume that when the cupula shrinks, the activity to stimuli is reduced and thereby caloric response.

The results in Paper IV showed a reduced caloric response in 65 % of the patients but the absence of caloric response on one side was not found in any of the patients. Only two patients have been recorded with high levels of decreased function at FU.

It can be suggested that the difference in degree of affection between the cupula and the sensory epithelia of the crista modifies the clinical features of vestibular disorders and the results of vestibular tests. Some of the patients had a previous history of canalolithiasis, which indicated peripheral disturbance. Some of them had reported recurrent vertigo of various duration and frequencies. Few of the patients who had recurrent position induced vertigo were without impairment in the vestibular tests, hypothetically indicating a minor alteration of cupula. We must also take in account one shortcoming of the caloric test i.e., it does not establish the sensitivity of the vestibular organs in absolute terms but only as difference in sensitivity between the two sides .

It was established that in the series of patients in study IV the function of the inner ear was altered, not only at a cupula level but also in the sensory structure of the otolith organ as demonstrated in the otolithic tests. Otogelin is one of the main proteins that form the cupula and that anchor the cupula base to the crista and also otolith membrane to the macula utriculi and sacculi [116-118]. In the absence of the otogelin gene in animal studies, the cupula is known to be detached from the crista. It can be speculated that detachment of whole and/or parts of otolith membrane, (not only the otoliths per se) is a possible cause of acute and residual peripheral disability found in our patients. In cats are a high proportion of vestibular neurons that receive convergent inputs from canal/otolith nerves [119]. It can be assumed that different morphological changes on cupula and/or the otolith membrane may distort the combined otolith-canal neural activity. However to our knowledge, it has not been recognized that horizontal nystagmus can be elicited from the otolithic organ per se.

"Cupula dysfunctions " as a part of a vestibular disorder

Careful neuro-otological examination is critical for differential diagnosis regarding positional vertigo. Besides the present studies we have followed patients with recurrent attacks of vertigo and both the nystagmus characteristics and the results of vestibular tests change from time to time.

One of the patients is representative of the group.

The patient, a male who was otherwise healthy, was admitted to the hospital suffering from severe vertigo and unsteadiness along with vomiting induced by head movements. Neurological examinations including MRT showed no abnormalities. On examination he had spontaneous nystagmus beating to the right. The nystagmus was of the same direction both in the supine and prone positions. The supine roll test revealed a persistent g-PDCN and the zero zone was 20° to the left. The next day he was submitted to vestibular tests, audiometry and ABR. Audiometry and ABR showed normal results. Caloric test showed symmetrical reactions but on a reduced level. In SVH a pathological result was recorded on the left side. Spontaneous and position induced nystagmus was the same as the previous day but in pronation nystagmus changed direction from right beating to left beating. He was examined with vestibular tests after 8 months at a time when he was without any subjective vestibular symptoms. A caloric test showed decreased reaction on the left side (CR=0,32). SVH and c-VEMP both had normal results. After two years he was admitted to the hospital again because of the same symptoms as his first hospital visit. He presented with a right beating spontaneous nystagmus in the supine head position, which changed to left beating in the prone position. No nystagmus was recorded in lateral head positions. Four months later he had an attack of vertigo with less severe symptoms than previous ones. In positional tests we found an apogeotropic nystagmus and nystagmus to the left in supine, upright and prone positions. Five years after the first admittance the patient was again submitted to vestibular tests. We recorded normal results in the caloric test, positional tests and SVH. However C-VEMP showed pathological results on the left side.

In addition to this patient we examined five patients, participating in the study that over the course from onset to follow-up demonstrated apogeotropic nystagmus in the positional tests. Another patient displayed g-PDCN both at a time with and without subjective symptoms but the SPV of g-PDCN was higher in the periods with subjective symptoms.

An interesting discovery was made following careful observation of nystagmus in patients with Meniere's disease. We noticed that during an attack of vertigo spontaneous nystagmus was prominent but as the nystagmus subsided it was followed by g-PDCN. Hypothetically this may indicate that the relative density between the endolymph and cupula has been affected and that the cupulae density becomes lower then the surrounding endolymph (J.Bergenius, personal communication).

Neurological examination of position-induced nystagmus is of high diagnostic value in the management of a patient with vertigo. The characterization of the positional nystagmus; fatigue, latency, direction and velocity with the help of video-nystagmoscopy gives important information about the different options, diagnosis and treatment of the positional vertigo. For example in the presence of a paroxysmal position induced nystagmus, repositioning manoeuvres are the treatment of choice.

However, in patients with persistent positional geotropic nystagmus treatment is lacking. The attacks of vertigo tend to be recurrent and vestibular tests may show pathological results. It is probable that the “light cupula” dizziness can be a symptom of peripheral vestibular deterioration.

Maybe is the time to take in consideration other pathophysiological mechanisms for positional nystagmus beside the “lithiasis” theory of freely moving debris.

CONCLUSIONS

Paper I

A persistent geotropic positional nystagmus indicates a dysfunction LSCC with a cupula of less specific weight than the surrounding endolymph. A zero zone was found with no nystagmus, beyond which the nystagmus changed direction when the head of the patient in the supine position was gradually rotated from side to side. The zero zone was present when the head was turned slightly towards one side and is thought to represent a position where the affected cupula is aligned with the gravitational vertical.

Paper II

A nystagmus pattern compatible with what is seen in patients with a light cupula in the LSCC could be partially demonstrated during the stage of PAN 1 in hemi-labyrinthectomized subjects. All subjects displayed a geotropic nystagmus that could be reversed when the subjects changed to the P position. However, the nystagmus pattern with the head straightforward in the P and S positions and the localization of the zero zone deviated from our observations in patients with a light cupula.

Paper III

After alcohol ingestion during PAN 2, unilateral deafferented subjects demonstrated a nystagmus that was apogeotropic and changed horizontal direction when the subject's head was changed from the supine to prone position or vice versa. The nystagmus pattern in a sideways position, and for the majority of observations with the head straight forward in both supination and pronation, concurs with what is described in patients with a heavy cupula (cupulolithiasis) in the LSCC, but is opposite to what is found in the hemi-labyrinthectomized subjects during PAN 1. In the S position, the nystagmus is directed towards the affected ear, while in the P position, it is directed towards the unaffected ear. The zero zone was the same for patients with heavy and light cupula and was recorded when the head of the subjects was turned towards the side with the affected cupula. It is hypothesized that the nystagmus pattern with the head straightforward in both S and P positions is dependent on the orientation of the long axis of the cupula in the LSCC. The SPV of the apogeotropic nystagmus was low.

Paper IV

The present study of patients with persistent geotropic nystagmus demonstrated frequent symptoms of subjective vestibular disability. Vestibular dysfunction in both the caloric and utricular tests was common and was persistent throughout the observation period. The nystagmus direction during the S or P position is not a reliable indicator of the affected side with the light cupula because different pathological processes can alter cupula orientation. Therefore, we propose that geotropic direction changing positional nystagmus is a sign of an inner ear disorder where the prominent clinical symptom is geotropic positional nystagmus elicited by a light cupula in the lateral SCC.

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