

Utricular and visual aspects of inner ear disorders

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I confirm that the experimental content within the thesis constitutes my own work. The information that has been derived from other sources, has been clearly indicated in the thesis and appropriately referenced.

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Abstract

The research described in this thesis is about investigation of the two less well understood mechanisms of balance system, namely utricular function and interactions of visual and vestibular system. Utricles are part of otolith apparatus and sense linear acceleration including gravity and lateral head tilts. Recent advances in rotational technology allow robust methods of assessment of unilateral utricular function using centrifugation techniques. Unilateral centrifugation generates substantial linear acceleration and the utricular response can be measured via tilt perception using subjective visual vertical (chapter 2). Utricular function was studied in common vestibular disorders seen in clinics, like chronic vestibular neuritis, benign positional paroxysmal vertigo, unilateral Ménière's disease, migraine and bilateral vestibular hypofunction. Bilateral vestibular hypofunction produced significantly low utricular gain (chapter 3). A detailed study of the utricular function of larger group of unilateral Ménière's disease showed significantly greater utricular asymmetry and lower utricular gain than normal controls. Interestingly, hearing loss was a predictor of utricular asymmetry (chapter 4). There was poor correlation between subjective measures and audiovestibular function. The chronic course of Ménière's disease is well known with slow decline over years and absence of correlation between symptoms and function may point to 'burn out' as long term phenomenon (chapter 5). An investigation into visual dependence and vertigo was performed to understand the effect of visual dependence on tilt perception in chronic vertigo. Individuals with vestibular symptoms can have increased visual dependency and migraineurs can have a non-adaptable increase in visual dependency (chapter 6).

In summary, we found that the unilateral centrifugation is a safe and well tolerated technique and provides additional, potentially useful information about utricular function. In future, the study of utricular function during acute phases of vertigo will further help overall understanding of otolith pathophysiology and mechanisms used for compensation.

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Abbreviations

AAO-HNS: American academy of otolaryngology-Head and Neck surgery Hearing and equilibrium subcommittee

AFS: Aural fullness scales

BPPV: Benign Positional Paroxysmal vertigo

BVH: bilateral vestibular hypofunction

CCW: counter clockwise

CP: canal paresis

CW: clockwise

cVEMPs: cervical vestibular evoked myogenic potentials

DHI: Dizziness handicap inventory

EC: eyes closed

ENG: electronystagmography

EO: eyes open

FLS: Functional level scale

MD: Ménière's disease

MSSQ: Short Motion Sickness Susceptibility Questionnaire Short Form

N; Normal

NegH: Negative Hallpike manoeuvre

oVEMPs: ocular vestibular evoked myogenic potentials

PosH: Positive Hallpike manoeuvre

PTA: Pure Tone audiometry

Rotn: disc rotation

SD: standard deviation

SEM: standard error of mean

SVQ: Situational Vertigo Questionnaire

SVV: subjective visual vertical

THI: tinnitus handicap inventory

UCF: unilateral centrifugation

UVN: Unilateral vestibular neuritis (chronic)

VEMPs: Vestibular evoked myogenic potentials

VM: vestibular migraine

VOG: Video oculography

VOR Vestibulo-ocular reflex

VSS: vertigo symptom scale

Chapter 1

General review of the balance system: anatomical structure and physiology

Our ability to maintain balance and stability is dependent on the complex interaction of multisensory inputs from vestibular system, visual system and proprioceptive system and further processing in the brainstem and cerebellum and higher cortical centres. The input is integrated in the brain stem (nucleus prepositus hypoglossi) and processed at further higher cortical centres for modulating visual and postural responses in response to sensory input and knowledge and interpretation of current context.

The vestibular component of the balance mechanism constantly interacts with the visual and the proprioceptive inputs and the three together forms the sensory input and feedback for the sense of stability or equilibrium and orientation (Shumway-Cook & Horak 1986). Head motion in all the three dimensions is mainly detected by the vestibular receptors in the inner ear. Visual system provides information on the position of the head with respect to its surroundings except in dark. Proprioceptors located in the muscles, tendons and joints feedback information on the position and movement of the head and the whole body with respect to the surroundings and support surface. This information is then processed in the central vestibular system together with visual and somatosensory inputs to result in awareness of head and body position and subsequent motor activity for continuing sense of equilibrium. Vestibular receptors in the human inner ear comprise of sensory organs for both angular and linear acceleration in the form of three semicircular canals and two otolith organs, namely saccule and utricle on each side. The most important function of the human vestibular function is the control of body posture by counteracting the constant pull of the gravity on the body. This is mainly dependent on reflexes generated by linear acceleration detectors, namely the otoliths. One of the other, equally important, function of the vestibular system is to

stabilise the image on the fovea of the retina especially when the head is not stationary, which the head is not most of the time (Grossman et al, 1988). The reflexes involved to facilitate this visual stabilising function is commonly called vestibulo-ocular reflex. Vestibulo-ocular reflex comprises of both the rotational (angular) and the translational (linear) components. Most of the natural head movements are a combination of rotational and translational movements in three different axes. Finally, maintenance of the muscular tone is also a major contribution of the human vestibular system and both semicircular canals and otoliths participate in this function.

1.1 *Brief anatomical structure of the peripheral vestibular system*

The peripheral part of the vestibular system is formed of hollow membranous sacs and tubes enclosed within the channels of the bony labyrinth. The bony labyrinth is incorporated in the petrous portion of the temporal bone. The term labyrinth was first coined by Galen in the 2nd century AD who first compared the inner ear anatomy to the curving passages of the legendary ‘Labyrinthos’ in Crete (Hawkins and Schacht, 2005).

Membranous labyrinth contains endolymph and the space between the periosteum of the bony and membranous labyrinth contains perilymph, supportive connective tissue and blood vessels. Endolymph has a density slightly greater than water and high concentration of potassium and lower concentration of sodium than perilymph (Anniko and Wróblewski, 1986). The main parts of the membranous labyrinth are the three semicircular canals, the otoliths organs including utricle and saccule and the membranous cochlea.

The three semicircular canals, a trio on each side of the head are membranous, approximately circular tubes aligned almost perpendicular to each other to form an approximately orthogonal coordinate system. The plane of the horizontal canal is slightly oblique and at an upward inclination of approximately 20° to the plane connecting the tragus to the lateral

canthus (Della et al, 2005). The two vertical canals are almost 90° to the plane of the horizontal canal (Della et al, 2005). This arrangement ensures that the combined signal from the 3 canals transduces head rotation in all 3 degrees of rotatory freedom.

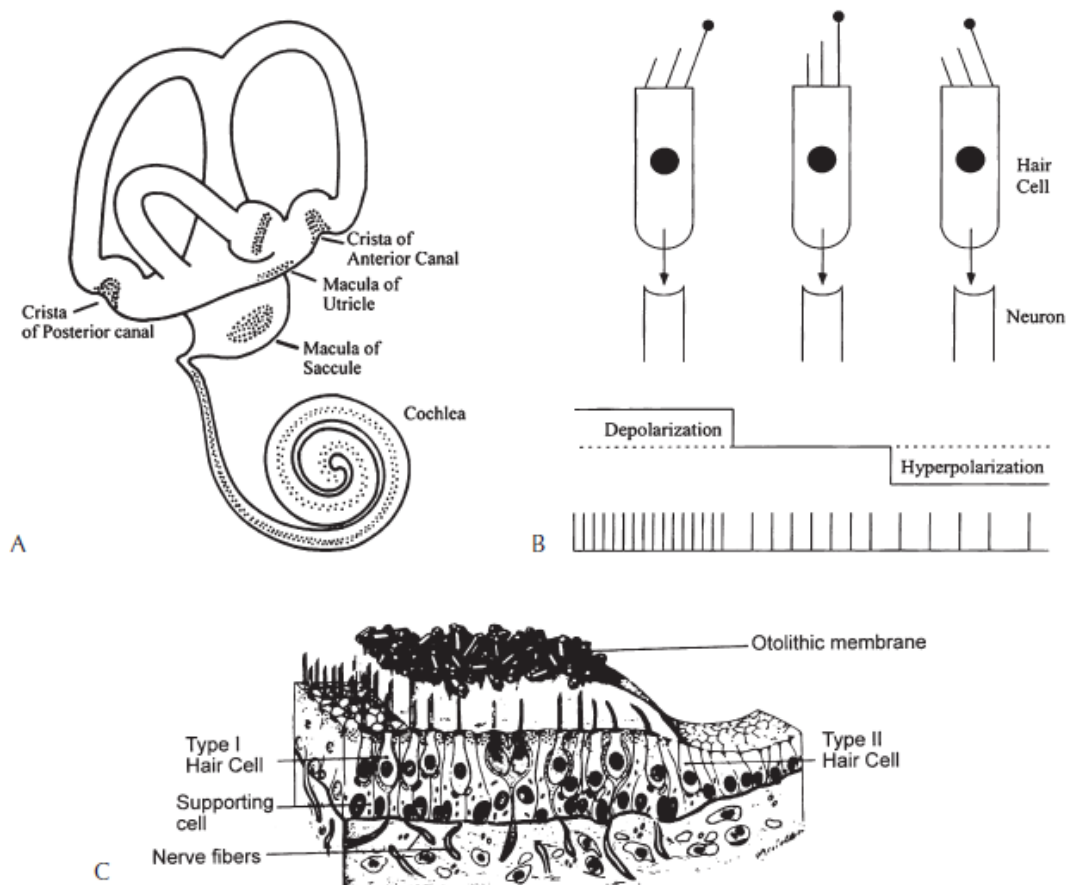


Fig 1.1 (from Leigh and Zee's the Neurology of Eye movements, 4th Edition, Page 26)

- A. Simplified diagram of the labyrinth with their receptors (labelled)
- B. Hair cells, showing basal firing rate in the vestibular nerve and increase/decrease depending on direction in which shearing forces act on the kinocilium (longest hair cell with beaded end)
- C. Otolithic membrane containing heavy crystals are covering the hair cells of macula

The otolith organs within the vestibule are formed of two membranous cavities namely utricle in the horizontal plane and saccule in the vertical plane. It is important to remember that all these vestibular organs are interconnected. Utricle is connected to the three semicircular canals by five openings. The horizontal canal is connected to the lateral wall of utricle by two openings. The two vertical canals share a common opening on the posterior side of the utricle but anterior parts of the two vertical canals open separately in the utricle. Saccule lies inferior to the utricle and is not in direct connection with the utricle. The saccule on the other hand directly communicates with the cochlea by the ductus reuniens and with the endolymphatic duct by the saccular duct. Utricular duct joins the endolymphatic duct at nearly the same level as the saccular duct and hence the endolymph of the saccule and the utricle do indirectly communicate.

1.2 Receptors for Acceleration

The Crista ampullaris within the semicircular canal is the receptor for rotational acceleration. Whereas the macula of the otolith organ detects linear acceleration and static tilt of the head (Fig 1.1A). Both the cristae and maculae contain specialised hair cells (which synapse with the axons the cell bodies of the vestibular afferents) which convert mechanical forces into neural impulses. There are two types of specialised hair cells called Type I and Type II hair cells. Type I hair cells have a calyx which Type II hair cells don't. The hair cells have numerous processes called stereocilia and a single kinocilium (Fig 1.1B). The hair cells exhibit a basal firing rate and changes in the firing rate from the basal rate helps perception of head acceleration (Goldberg and Fernandez, 1971).

In the semicircular canals, the processes of the cristae are embedded vertically in a gelatinous structure called the cupula. Each semicircular canal has a promontary at one end called ampulla. Ampulla houses the crista with the overlying gelatinous cupula. Crista and cupula

lie together in the middle with endolymph of the semicircular canal and separate it from the utricle and the vestibule. With every head turn, there is movement of endolymph which deflects the cupula and change the basal firing speed of the hair cells at its base (Goldberg and Fernandez, 1971). If the stereocilia is deflected towards the kinocilium, there is excitatory response (depolarisation), whereas inhibitory response (hyperpolarisation) is generated with deflection of the stereocilia away from the kinocilium (Fig 1.1B). The excitatory response induces an increase in the tonic firing rate on the vestibular nerve that is innervated by the hair cells. Inhibition causes a decrease in the tonic firing rate and is perhaps better thought of as a disfacilitation since hair cells cannot signal below a zero firing rate. Therefore, because the tonic firing rate cannot fall below zero there is thus a limit to how much the hair cells can signal rotation in their 'off' direction. In horizontal canals, movement of the endolymph towards the ampulla causes excitatory response. On the other hand, in the vertical canals, movement of the endolymph towards the ampulla causes hyperpolarisation or an inhibitory response. Furthermore, each semicircular canal responds best to the motion generated in its own plane (Goldberg and Fernandez, 1971). When head turns to one side, the semicircular canal of the same side is stimulated and the paired semicircular canal of the opposite side is inhibited (so called push-pull principle.) The detection of rotational acceleration only takes place for changes of velocity. If the subject is rotated at a constant velocity with no change in acceleration there will be no further cupular response till further acceleration or deceleration is generated. The time constant for cupula to return to its original position is approximately 4 s ((Dai et al, 1999) but the central velocity storage mechanisms prolong the time constant to 17s (Cohen et al, 1981; Leigh and Zee, 2006).

Macula: Both the otoliths, the saccule and the utricle contain macula as their sensory organ. The macula is a curved structure, less than a square mm, containing hair cells. The macula is covered with a heavy otolith membrane into which the cilia of the macular hair cells are

embedded (Fig 1.1C). Otolith membrane contains heavy calcium carbonate crystals, also called otoconia. The specific gravity of the otoconia is thus higher than the endolymph which generates inertia making it particularly responsive to gravity and linear acceleration. During head tilt or linear acceleration, thus there will be a differential movement of the macula and the otolithic membrane causing activation of the sensory hair cells.

1.3 Brief neural substrate of the vestibular system

The neural arrangements of the vestibular systems and interconnections are quite complex. A brief and simple overview is described. The primary vestibular afferents have cell bodies in the Scarpa's ganglia in the internal auditory canal. There are two divisions of the vestibular nerve- superior and inferior. The superior division supplies the horizontal and anterior semicircular canals and the utricle. And the inferior division supplies the posterior semicircular canal and the saccule. The central axons of the two divisions travel together to brainstem where the superior division form central synapses in the superior vestibular nerve and the cerebellum (Leigh and Zee, 2006). The inferior division pass to the medial, lateral and inferior vestibular nuclei. The afferent signals from vestibular nuclei are relayed directly to the extraocular motor nuclei (vestibulo-ocular reflex), to the spinal cord, cerebellum. The cortical projections of the vestibular system are less well defined and believed to be in the parieto-insular region of the cerebrum (Kirsch et al, 2015).

1.4 Vestibular reflexes

Vestibular reflexes play major functional role in stabilising gaze, controlling posture and maintaining skeletal muscle tone.

Vestibulo-ocular reflex (VOR) is mainly responsible for visual gaze stabilisation both during passive displacements of the head and active movement (Cohen and Gizzi, 2003). VOR is a

short latency three neuron reflex composed of vestibular ganglion, vestibular nuclei and the oculomotor nuclei (Ito 1975, Leigh and Zee 1999a). VOR generates rapid compensatory eye movements to stabilise the image on the fovea of the retina during head movements. These compensatory eye movements are opposite in direction to the movement of the head but with equal velocity. Three types of VOR have been defined based on the type of head movement. Angular acceleration of the head is detected by semicircular canals (Fig 1.2) and through a brainstem reflex arc generates the angular VOR whose function is to stabilise visual images on the fovea.

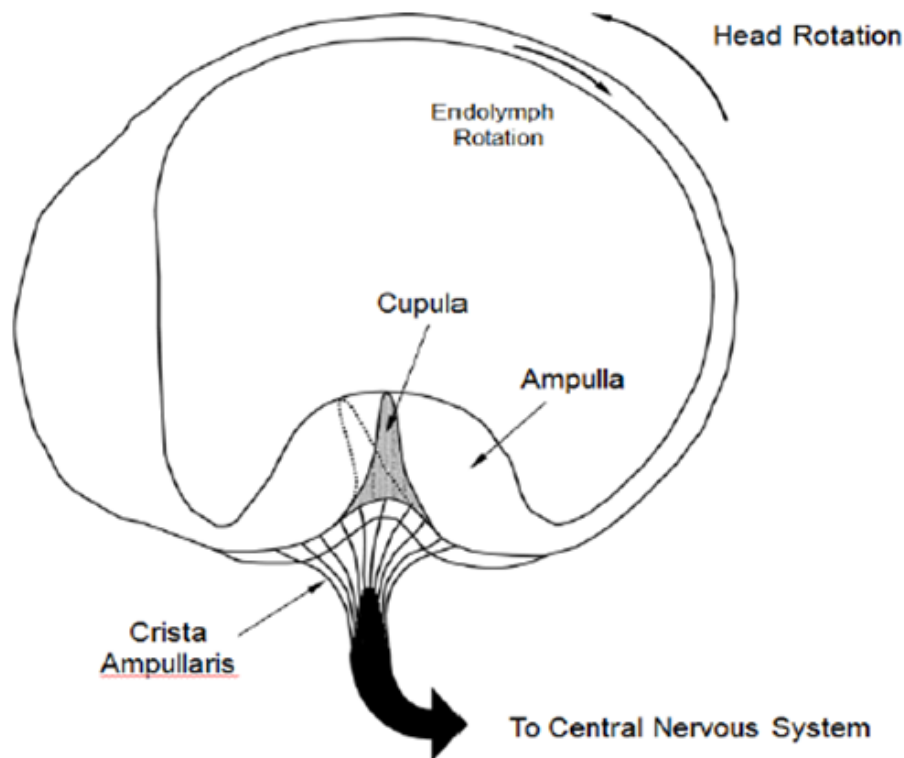


Fig 1.2 (taken from the Academic Department of Neuro-otology archives)

The simplified diagram shows the movement of endolymph in response to rotation of the head. The endolymph movement causes cupula to deflect leading to change in the baseline or 'tonic' firing rate of vestibular axons, generating the vestibulo-ocular reflex.

Linear acceleration, on the other hand, produces linear VOR by stimulating the otolithic organs. The natural head movements are not specific of any type of acceleration and thus concurrent activation of angular and linear VOR stabilises visual gaze. There is a third type of VOR described as ocular counter-rolling during lateral head tilt with respect to gravity. Ocular counter-rolling is a torsional movement of the eye around the line of sight, a term first introduced by Bárány in 1906 (Simonsz, 1985). Torsional deviation of the eyes in response to 60-75 degrees of static head tilt is 6-8 degrees (Miller and Graybiel, 1963). Hence, the eye movements generated by relatively large tilts of the head are of sufficiently small magnitude to comment that ocular counter rolling in real life is a vestigial response with little compensatory function. Additionally, although not addressed in this thesis, it should be borne in mind that vestibulo-collic and vestibulo-spinal reflexes generate compensatory responses in the neck, spinal and limb muscles to stabilise the head and body posture and muscle tone.

Chapter 2

Areas of Research and Questions

The thesis describes the two less well understood mechanisms of the complex balance system, the otolithic (mainly utricular) apparatus of the vestibular system and the interaction of the different components (mainly visual and vestibular). The next three experimental chapters describe the study of utricular function in common peripheral vestibular disorders with main emphasis on Ménière's disease. The final experimental chapter discusses the interaction of vestibular and non-vestibular components, mainly the effect of visual dependency on the balance system.

The study of utricular function is important in many ways apart from the longstanding interest of the scientific community and recent technological advances making it feasible to study the same. The symptoms of otolith disorders can vary from non specific and vague descriptions of 'tumbling', 'walking on pillows', 'room tilt' illusion, vertical diplopia (unexplained by extraocular muscle palsy), unexplained body lateropulsion, unexplained falls, falling sensation when going down in lift and others (Gresty et al,1992). And on the other hand, otolith dysfunction has been well recognised as in Tumarkin's otolithic crises in Ménière's disease or otolith Tullio phenomenon (ocular tilt reaction to loud sounds). Further investigations into studying all aspects of vestibular function will help towards a more useful and informed classification of the vestibular symptomatology and guide future directions of treatment and rehabilitation.

A further consideration is that there is a constant interaction of the three main sensory components of the balance system and it is not known if this complex visuo-vestibular interaction changes following a vestibular insult and how adaptation takes place (Roberts et al, 2013). Following an acute unilateral vestibular lesion, there are central mechanisms which

help individuals to compensate for their loss and regaining near normal function and this process is called adaptation. However, recovery can be prolonged in certain individuals suffering similar vestibular insults and it is speculated that one of the possible factors is due to varying degrees of visual dependency in these individuals (Bronstein AM, 2004).

Hence, the comprehensive testing of the less well recognised areas of the balance system will help to further understand the organic basis of these symptoms, understand how compensation following damage to these structures take place and perhaps help in the development of new methods of vestibular rehabilitation for this group of patients.

Specific investigations undertaken in this thesis

- i) A study of otolith function conducted in a generalised group of patients with a variety of vestibular disorders. This seeks to establish the general utility of otolith testing and obtain some idea of the prevalence of otolithic disorders.
- ii) A specific application to investigating Ménière's disease and its symptomatology allows correlation of otolith function with patients' subjective ratings of symptoms.
- iii) A study of visual dependency function in BPPV was undertaken as a particular opportunity to investigate the impact of a brief attack of vertigo on the development of visual dependency.

Functions of the otoliths and techniques for evaluating otolith pathophysiology in human subjects.

In this section, a brief overview of the function of otolithic apparatus and its assessment with description of the unilateral centrifugation technique used in subsequent experimental chapters will be illustrated.

Physiology of otolith apparatus

The otolith organs are receptors mainly for linear acceleration including gravity (Fernandez and Goldberg, 1976). The hyperdense curved macula of the utricle and the saccule is primarily oriented in horizontal and parasagittal planes respectively. The varied orientation of the macula in both the otolith organs is useful in transducing responses to translational head movements in various directions. The saccular macula is oriented in mainly vertical plane and nearly orthogonal to the macula of the utricle. This makes saccular macula generate responses during up and down translations of the head. Based on the mainly horizontal orientation of the macula, the utricle is most sensitive to linear acceleration in the horizontal plane of movement including side to side translations and head tilts. The lateral part of the macula of utricle is more sensitive to side to side translations and mainly responsible for the linear vestibule-ocular reflex (Angelaki and Dickman, 2003). However, the head tilts relative to gravity are predominantly sensed by the medial part of the utricle and responsible for compensatory ocular counter-rolling via torsional eye muscles (Lempert et al, 1998).

Maculae also respond to linear acceleration generated during rotational movements of the head (centrifugal and tangential accelerations) because of its eccentric location to the axes of rotation of the head. Thus linear acceleration produced either by translation or by rotatory motion is effective in stimulation of the otolith end organs. Otolith ocular reflex produces eye movements that maintain gaze stability during linear head movements. There are three possible directions for linear movement of the head, namely, horizontal (side to side); vertical (up and down) and front to back. In reality, none of the eye or head movements are purely in one single plane of movement and information from canals, otoliths, visual and proprioceptive signals are jointly processed in the brainstem and higher order centres to process correct output signals for stability and equilibrium.

Methods of investigating otolith function

There has been a long process of research for the development of utricular function testing and current research interest is directed to develop robust and comprehensive assessments of unilateral utricular function. A brief outline of the different methods will now be presented followed by detailed description of the unilateral centrifugation technique which has been used to measure unilateral utricular function in this thesis.

Tangential acceleration of the head has been successfully generated by eccentric positioning of the head on a rotating chair used for canal VOR testing. Thus, the subject sits on a conventional rotating chair while bending forward and the head is tightly secured onto an eccentric chin rest producing head eccentric rotation (Gresty & Bronstein 1986, Gresty et al 1987). The VOR thus generated during eccentric head rotation is subtracted from VOR generated during conventional head rotation which broadly is representative of otolith VOR. There can be approximately up to one third increases in VOR responses when both canal and otolith responses are combined using eccentric head positioning technique. The limitation of this technique was that both the sides were stimulated at the same time and otolithic responses were mixed with canal responses. Also attempts were made to generate linear acceleration (in dark) along inter-aural axis by using electrically driven motor powered linear sleds with head fixed (Lempert et al, 1996) but limited by the amount of linear acceleration which can be generated.

Other methods of measuring otolith function include off vertical axis rotation with respect to gravitational vector. The chair and the subject are tilted vertically with respect to earth vertical which enables continuous stimulation of the otoliths during rotation of the tilted chair. The otoliths are stimulated during off vertical axis rotation as they have to continuously reorient to the gravity vector (Koizuka 2003). In extreme cases, the chair is rotated at earth

horizontal axis also called 'barbecue rotation'. The eye movements are recorded using conventional VOG recordings and are elicited by otolith stimulation after chair reaches constant velocity. The main drawback of this technique is that it is poorly tolerated due to intense nausea (Dai et al, 2010).

Static head tilts are another method to generate otolith ocular responses also known as ocular counterrolling. Static tilts can be generated sophisticatedly using gimbals systems and recording of eye movements using 3D-VOG. (Diamond and Markham 1983).

Further research and understanding of the effect of the unfamiliar gravitational conditions as in parabolic flights led to next course of research into development of otolith function tests. The asymmetry of the so called 'earth normal' vestibular system was speculated as the main contributing factor to space motion sickness (Parker 1998; Diamond and Markham, 1992; Nooji et al, 2011). The difficulty of testing this hypothesis of utricular asymmetry independent of canal function was a major drive to develop differential stimulation of one utricle at a time by Wetzig et al, 1990. The original method of unilateral testing of utricular function by adding a centrifugal force to the constant gravitational force has been further refined and various paradigms developed (Clarke et al, 2003; Wuyts et al, 2003; Schonfield and Clarke 2011).

Investigation of otolith pathophysiology

A brief overview of the paradigms used in previous studies is briefly described below with summary of their findings. Clarke et al, 2003 studied utricular function utilising the unilateral centrifugation technique using a modified rotatory chair to generate linear acceleration to stimulate the labyrinths. The rotating chair is displaced 3.5-4cm from the centre and thus displacing the labyrinths from the centre of rotation. The utricle which is eccentric is exposed to centripetal acceleration (240-400deg/s) resulting in unilateral stimulation from the

resultant gravito-inertial tilt (11deg). The utricular responses were measured using SVV. They found that responses were consistently diminished in 5 patients (with vestibular nerve completely sectioned undergoing surgical treatment for acoustic neuroma) on the affected side. Schonfield and Clarke in 2011 used the same paradigm but they attempted to further classify the SVV responses as different degrees of under estimation and over estimation of the SVV.

Wuyts et al, 2003 also used similar paradigm for unilateral centrifugation but chair displacement was 4cm and chair velocity was 400deg/sec resulting in higher gravito-inertial tilt of 21.7 deg. They collected eye movement recordings using 3D-VOG recordings. The experiments were done on 28 normal subjects and 14 patients who had undergone surgery for acoustic neuroma. As expected, there was reduced utricular sensitivity in the patient group.

Since the vestibular apparatus supports spinal reflexes it follows that some method of stimulating the peripheral vestibular apparatus may allow the observation of myogenic responses in skeletal muscle. This possibility is exploited in the development of the Vestibular evoked myogenic potentials (VEMPs). VEMPS provide yet another way of measurement of otolith function without using rotational testing. Saccular testing using cVEMPs has become widely popular since first description approximately two decades ago (Colebatch et al, 1994). Different stimulus can be used to elicit myogenic potentials and more recently bone conducted vibration were found to elicit such responses from extra-ocular muscles (Rosengren et al, 2005). These extra-ocular responses to bone conducted vibration have been vigorously studied (Iwasaki et al, 2007; Welgampola et al, 2009; Govender et al, 2009; Weber et al, 2012) and now believed to be predominantly utricular in origin. oVEMPs have the advantage of simple setup and has the potential to play complementary role in vestibular assessment (Weber and Rosengren, 2015).

2.1 General Methods used in the present studies:

There follows a detailed description of the unilateral centrifugation technique which followed on from this research and has been used in our study.

Subjects were securely seated on a rotating chair (Neuro Kinetics Inc, Pittsburgh) which slowly accelerated in darkness about a vertical axis to reach a constant velocity of 400°/s.

During the constant velocity rotation, the subject was shifted slowly sideways relative to the rotation axis, up to 4.2cm to the right and left. The subject was held for 30s in the three test

positions, rotating chair laterally displaced to the right, rotating chair centred on axis of rotation, rotating chair displaced to the left.

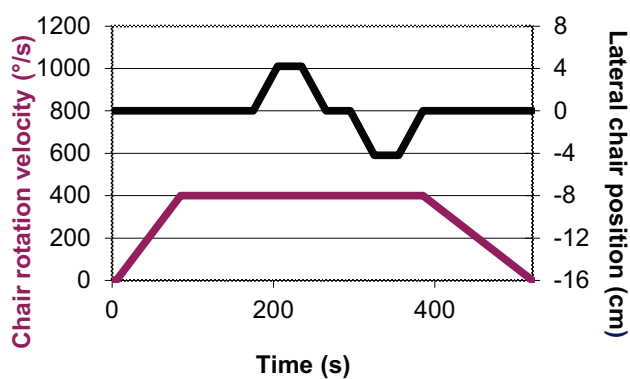


Fig 2.1 showing chair velocity and its position with time

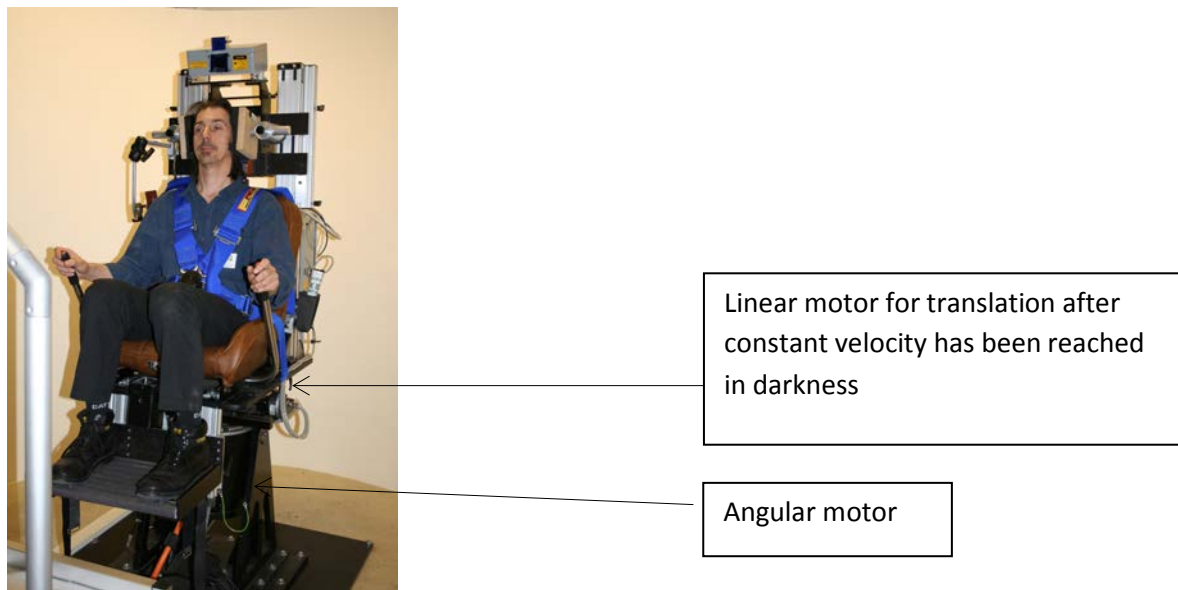


Fig 2.2 Photograph of the modified rotating chair used for unilateral centrifugation with a subject securely seated.

Centripetal acceleration of the utricles modifies the perceived gravitational vertical, and so changes in the subject's position relative to the rotation axis will generally induce sensations of roll tilt. This roll tilt was measured using a chair-fixed subjective visual vertical (SVV). The subject used a rotating knob to orientate a randomly offset laser line (160mm x 3mm) to the perceived gravitational vertical; approximately 8 settings were made in each test position and the median value was taken to indicate the subjective roll tilt. Subjects also performed the SVV task when the chair was stationary (Static SVV). The SVV values when the chair was rotating are demarcated as dynamic SVV for the respective chair position, for example, Dynamic SVV on Right centrifugation, Dynamic SVV on centre rotation and Dynamic SVV on Left centrifugation.

In each extreme chair position, the net acceleration on the head (gravitational and centripetal) was equivalent to a roll tilt of 11.7° , in opposite directions for the Right and Left chair positions.

‘SVV gain’ was defined as the difference between the SVV tilts in the Right and Left positions, divided by 23.3°.

Utricular ‘asymmetry’ was defined by comparing the mean SVV tilt in the three test positions (relative to the Static value) to the difference between the Right and Left SVV settings. A complete unilateral loss would be expected to produce zero SVV tilts when the remaining functioning utricle was positioned on the rotation axis. In this case, the mean SVV tilt would be equal to half the maximum range (100% asymmetry). Further details of the analysis can be found in appendix V (page 118).

Utricular asymmetry and Utricular gain were calculated by the following equations:

$$\text{Utricular Asymmetry \%} = -200(\text{mean of SVV R,C,L}) - \text{static SVV} / \text{Left SVV} - \text{Right SVV}$$

$$\text{Utricular gain} = (\text{Left SVV} - \text{Right SVV}) / 23$$

In this thesis, we describe particularly the findings of utricular function using the unilateral centrifugation technique in different groups of patients with most common vestibular diseases seen in our clinics: patients suffering from chronic unilateral vestibular neuritis (UVN), Benign Positional Paroxysmal vertigo (BPPV), Ménière’s disease (MD), Migraine and bilateral vestibular hypofunction (BVH).

2.2 Aims of the study of utricular function

The aims of the study of utricular function were:

- (1) to assess the feasibility of using unilateral centrifugation technique to assess utricular function in patients with peripheral vestibular dysfunction,
- (2) to investigate the value of utricular function tests to provide additional information regarding vestibular function in above patients, and

(3) to investigate clinically the use of this additional information to understand some of the symptoms in these patient groups.

The study had ethical approval from St. Mary's Research Ethics Committee (Ref No. 08/H0712/95) and research governance approval from Imperial College Healthcare Trust (ref No. BROA2010). And the individual participants of the study also signed informed consent form for voluntary consent.

Chapter 3

Utricular function in general vestibular disorders

3.1 Introduction

Vestibular disorders are quite common (lifetime prevalence 7.4% Neuhauser et al, 2005) but can present in a significantly alarming way both to the patients and clinicians. However, skilful history taking and bedside examination helps to differentiate between serious and benign disorders (Seemungal and Bronstein, 2008). Functional evaluation and radiological imaging are also helpful guides to further interventions and procedures. Vestibular rehabilitation forms a core component of therapy irrespective of the treatment chosen (Bronstein and Pavlou, 2013). For a specialised clinician experienced in dealing with vestibular disorders, the road map is usually clear except that there are some gaps of knowledge of vestibular function even in the common or general vestibular disorders. Arguably, the vestibular abnormalities do not limit to the parts of labyrinth which are more accessible to testing but can affect any unit of the end organ.

The vestibular system has been known to be both complex and inaccessible, a true labyrinth, making it one of the most challenging systems to be investigated in the human body. The challenge has been to develop tests which generate robust data on one hand, as well as are safe and well tolerated by the patients on the other. The testing of horizontal canal function using caloric tests and manual rotating chairs marked the beginning of the era of functional evaluation of vestibular organs by Bárány approximately hundred years ago (Bárány 1907, Bárány 1914). With further development of knowledge of the vestibular system and application of technological advances, we have now improved understanding of the individual units of the vestibular end organs. For example, video head impulse testing for horizontal or vertical semicircular canals (Halmagyi and Curthoys, 1988; MacDougall et al,

2009) or cervical vestibular evoked myogenic potential testing for otolith (predominantly saccular) testing (Brantberg 2009, Rosengren et al, 2010). Despite these significant advances, the knowledge of the utricular function even in the common disorders has been elusive.

Otoliths (utricle and saccule) respond to linear acceleration, including gravity, in different planes (Fernandez & Goldberg, 1976). Although both utricular and saccular maculae are sensitive to multiple planes of linear acceleration but utricles are predominantly sensitive to horizontal (right-left) motion. Rotational techniques have been routinely used for to evaluate vestibular system, for example, electronystagmography for horizontal canal function. Further advances in rotational technology in the last two decades has led to linear acceleration being generated safely, by translating a rotating chair on a dual axis motor, after canal responses have subsided. Unilateral centrifugation is one such paradigm which generates one sided utricular responses and can give us useful information on functioning of the utricular organs.

Vestibular function assessment forms the cornerstone of diagnosis in patients presenting with nystagmus, dizziness or imbalance which represent potentially neurotological disorders. In common disorders like vestibular neuritis, BPPV or bilateral vestibular hypofunction it is useful to record the level of function of the different parts of the vestibular system. Apart from the clinical and academic interest in the pathophysiology of these disorders, rehabilitation programmes can be planned based on the deficits of individual components to aid central compensation and recovery in peripheral disorders.

Marom et al (2009) in his critical review of pathophysiology of BPPV reminded that even though it is the most common vestibular disorder and one which can be so well treated, the understanding of vestibular physiology even in BPPV is far from complete (Marom et al, 2009). The role of otoliths has been speculated in BPPV both due to presence of vertical components of nystagmus (Hayashi et al, 2002) as well as in post treatment dizziness (von

Brevern et al, 2006; Seok et al, 2008). Another common scenario is where there is significant symptom overlap, for example, Ménière's disease vs vestibular migraine, studying novel methods of vestibular function can aid in further understanding the differences or similarities between the two disorders (Radtke et al, 2002). In a study of otolith function using VEMPs in both these disorders, two thirds of patients in both groups had similarly reduced amplitudes and no difference in latencies suggesting an otolith link between the two (Baier and Dieterich, 2009). Furthermore, Ménière's disease is commonly a progressive disorder and usually starts at the cochlea-saccular part and gradually involve utricle and then semicircular canals as noted on temporal bone studies (Okuno and Sando, 1987).

However, it has been technically difficult to study utricular function in details even in these common vestibular disorders because most vestibular stimuli involve both canal and otolithic stimulation so that results may be equivocal for otolith versus canal dysfunction. This chapter attempts to address the current lack of knowledge of utricular function in common vestibular disorders by studying the utricular function using advanced rotational techniques to generate linear acceleration. This brings us up to date with more comprehensive information on utricular function in common vestibular disorders of what has been elusive so far. It can only be helpful for both researchers and clinicians to know how the system is performing as a whole even in common disorders. Furthermore, rehabilitation techniques can be appropriately developed, planned and targeted to the individual patient based on this more detailed understanding of the overall level of vestibular dysfunction.

3.2 Materials and methods

Experimental strategy: Utricular function was studied in normal controls and in patients with common vestibular disorders. All 56 control subjects were free of any audio vestibular abnormalities and participated voluntarily in this study.

Patient groups: Utricular function was investigated in different groups of patients presenting with common vestibular disorders in the Neurotology clinics in Charing Cross Hospital which provide a tertiary referral service, London following their voluntary written consent (after providing verbal and written information of the experimental technique). Five different groups of vestibular patients were studied and the standard clinical criteria were used for the diagnosis of their disorders and have been summarised below. The exclusion criteria for all the patient groups were subjects with previous history of any other confounding peripheral vestibular disorders or neurological diseases. Pregnant women were excluded from rotational testing due to safety reasons. The subjects were fully aware that they were free to withdraw from the study at any time. The study had approval from St. Mary's Research Ethics Committee (Ref No. 08/H0712/95) and Imperial College Healthcare Trust Research governance office (ref No. BROA2010).

The brief description of diagnostic criteria used in different patient groups is as follows.

Chronic vestibular neuritis group: Unilateral vestibular neuritis presents as an acute episode of intense vertigo, unsteadiness, nausea and vomiting, sometimes following a simple upper respiratory tract infection. The patients had undergone full clinical examination and audiovestibular testing, including PTA and bithermal caloric testing to confirm the diagnosis during the acute stage. Following written consent, utricular function was investigated during the chronic stage of their illness (after 6 months of the initial diagnosis).

Vestibular neuritis is the most common cause of acute episode of prolonged vertigo (Jeong et al, 2013). The incidence of vestibular neuritis is approximately 3.5/100,000 population as per epidemiological surveys (Sekitani et al, 1993). Literature review suggests that the epidemiological figures were mainly derived from patients seen in hospital setting with lack

of sufficient data from the community patients (Murdin and Schilder, 2015). The true incidence is probably higher.

BPPV group: BPPV is the single most common presentation of the peripheral vestibular disorders with just under half the patients being provided the diagnosis in dizzy clinics (Bath et al, 2000). BPPV is characterised by episodes of brief spells of vertigo, lasting less than a minute and provoked by change in head position (turning in bed, lying down, head extension). The diagnosis is clinical based on the classical symptoms and typical nystagmus on Dix-Hallpike manoeuvre (Dix and Hallpike, 1952; Kaski and Bronstein, 2014). Posterior semicircular canal was affected in all the BPPV patients participating in this study.

Unilateral Ménière's disease group: Only definite unilateral Ménière's disease patients were included in the study. As per American Academy 1995 guidelines, definite Ménière's disease is diagnosed when there are more than two episodes of definitive spontaneous vertigo attacks lasting more than 20 minutes, confirmed hearing loss in the affected ear with reported fullness and/or tinnitus in the same ear with other disorders excluded (Committee on Hearing and Equilibrium, 1995). Eight patients were in stage 3 based on their hearing loss and remaining were in stage 2. These patients did not have satisfactory response to conservative treatment and hence were suffering from refractory Ménière's disease. Patients with bilateral Ménière's disease were not included in the study.

Bilateral vestibular hypofunction group: The patients were diagnosed with bilateral vestibular hypofunction if the total canal response (sum of all four smooth pursuit velocities) were less than 20deg/sec. The tympanic membrane was checked for a flushed appearance after warm water irrigation to confirm that the membrane had been heated by adequate irrigation.

Vestibular migraine group: Vestibular migraine was diagnosed clinically based on as per Neuhauser and Lempert criteria proposed in 2009 with clinical examination and investigations including MRI being normal. This is an interesting group to study the utricular function as they show wide variety of vestibular symptoms. There were 3 patients with definite vestibular migraine and 13 patients had probable vestibular migraine. Vestibular migraine is not an uncommon disorder with a prevalence of 7-9% in specialist clinics (Neuhauser et al, 2001). The lifetime prevalence of vestibular migraine is estimated as 0.98% (Murdin and Schilder, 2015). 12 of the vestibular migraine patients in this group were on standard migraine prophylaxis treatment (propranolol, amitryptiline, pizotifen, topiramate) .

The details of the patient population in different groups has been shown in Table 3.1 and further described in section 3.3c.

Specific Methods of testing:

Utricular function was measured using unilateral centrifugation technique (details of the technique in the previous chapter) in both normal controls and in the selected patient groups. In addition to the study of primarily utricular function, different groups have been investigated with additional standard battery of audio vestibular tests. Additional assessments were included specific to the individual patient group which opportunistically addressed interesting research questions relevant to the vestibular disorder.

The following demographic table summarises the different experimental groups of subjects:

Group	n	Age (range in yrs)	Age (mean, sd in yrs))	Female	Male	Right sided disease	Left sided disease
Normal (N)	56	18-80	44.7, sd 17.9	20	36	n/a	n/a
unilateral vestibular neuritis (UVN)	10	35-78	51.8, sd 15.7	7	3	5	5
unilateral Ménière's disease (MD)	10	40- 67	50.5 sd 7.5	6	4	5	5
Bilateral vestibular hypofunction (BVH)	7	24-78	48.9 sd 19	3	4	n/a	n/a
Benign Positional Paroxysmal vertigo (pBPPV)	10	45-85	63.4, sd 12.3	5	5	7	3
Vestibular Migraine	16	20- 68	41.3, sd 13.1	11	5	n/a	n/a

Table 3.1 Demography of the subjects in different experimental groups

This has been done for two reasons:

- a) to validate the protocol for unilateral centrifugation technique of utricular function in our laboratory (e.g. correlations with other audio-vestibular tests), and
- b) to explore the varying nature of abnormalities in individual groups in a disease specific manner.

Chronic vestibular neuritis group:

In the chronic vestibular neuritis group, we studied their symptom load using validated questionnaires, namely dizziness handicap inventory was performed. (Jacobson and Newman, 1990, appendix I). This was to observe if objective utricular abnormalities correlate with their

subjective symptoms which can be long standing and troublesome in up to 50 % of vestibular neuritis patients (Kammerlind et al, 2005). The Dizziness Handicap inventory is a self reported measurement of dizziness perceived by the individual. It has 25 items measuring the functional, physical and emotional aspects of balance and dizziness and is commonly used to report self-perceived outcomes of vestibular recovery (Mutlu and Serbetcioglu, 2013). DHI has high internal consistency (Cronbach's $\alpha = 0.91$) and high test-retest reliability (Pearson's product moment correlation = 0.97).

Patients also underwent bithermal caloric testing for assessment of the canal function. In caloric test, the patient is laid supine with head tilted 30° upwards and external auditory canal is irrigated with cold water (30°) and warm water (44°). The resultant nystagmus is measured and canal paresis calculated using Jongkees formula (Jongkees et al, 1962).

BPPV group:

In this group, the utricular function was studied twice, firstly after diagnosis with Dix-Hallpike manoeuvre and then immediately after treatment. This was to gain further understanding if repositioning of the utricular debris made any difference to their utricular function (Seok et al, 2008).

Unilateral Ménière's disease group:

In addition to the pure tone audiometry and MRI Brain scan which are essential for the diagnosis as per Committee of Hearing and Equilibrium guidelines (AAO-HNS criteria, 1995). The patients underwent bithermal caloric testing which was then correlated with utricular function assessed by the unilateral centrifugation technique.

Bilateral vestibular hypofunction group: These patients were tested with full battery of routine audiovestibular testing, including pure tone audiometry, bithermal caloric tests and

rotational ENG. They also underwent blood tests as per standard clinical guidance to rule out possible autoimmune causes of their vestibular loss.

Vestibular migraine group: As there can be overlap of symptomatology between Ménière's disease and vestibular migraine, standard audiovestibular tests were performed to rule out any concurrent disorders. Patients with vestibular migraine can present with auditory symptoms similar to Ménière's disease like unilateral tinnitus, fluctuating hearing and audiometrically documented low frequency hearing loss (Baloh, 1997; Shepard, 2006). The vertiginous symptoms in both the conditions can be confusingly similar (Shepard, 2006; Gürkov et al, 2014).

3.3 Results

3.3a Utricular function in normal control subjects:

The utricular function of 56 healthy subjects (20 females and 36 males) was studied. All subjects in the control group were assessed clinically for no audiovestibular or neurological diseases. The age range of this group varied from 18- 80 yrs (mean 44.7yrs sd 17.9yrs) to match with the age group of our various patient groups. Fig 3.1 shows the mean SVV values for the different conditions including static SVV, dynamic SVV on centre rotation, dynamic SVV on left centrifugation and dynamic SVV on right centrifugation. From the individual SVV values of each participant for each condition, individual utricular asymmetry and individual utricular gain were calculated by using the formula described in the previous chapter and in the appendix V whose value is to characterise asymmetry in a single value. The mean Utricular asymmetry was $-3.05\% \pm \text{sd } 41.456$ and mean Utricular gain = $0.658 \pm \text{sd } 0.302$. Utricular Asymmetry and gain were normally distributed in the normal subject group (Fig 3.2).

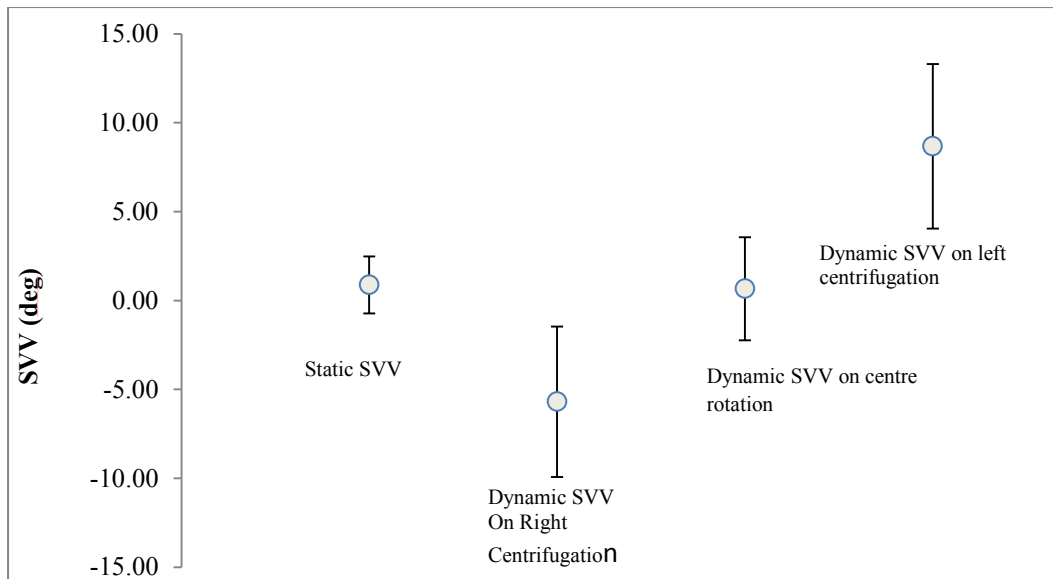


Fig 3.1 Static & Dynamic SVV in Normals (n=56) (*Mean with Standard Deviation*)

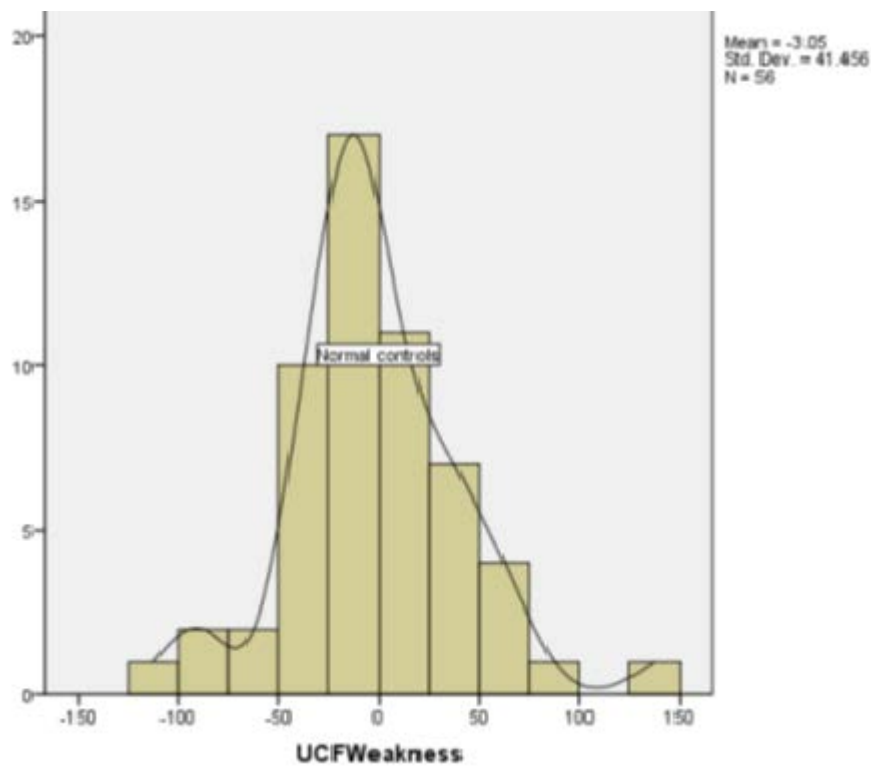


Fig 3.2 Utricular Asymmetry in normal population. (UCF weakness in this figure is same as utricular asymmetry)

3.3b Utricular function in different patient groups

A one way ANOVA between groups was conducted to compare the mean values of the normalised utricular asymmetry of the normal group, unilateral vestibular neuritis group, BPPV group, Ménière's disease (MD) group, Migraine group and bilateral vestibular hypofunction (BVH) group. There was a statistically significant difference in normalised Utricular asymmetry between groups as determined by the one-way ANOVA [$F(5,103)=3.89$, $p = 0.003$].

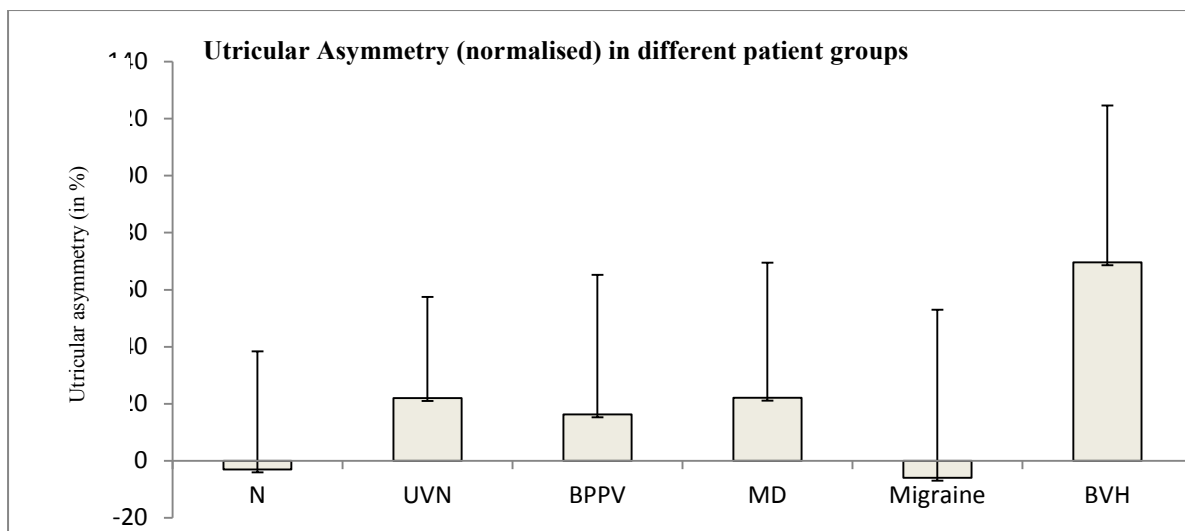


Fig 3.3 Utricular asymmetry (normalised) in different groups

Post hoc analysis (Tukey HSD) showed that the Utricular asymmetry in the small group of patients with bilateral vestibular hypofunction (69.57%, sd 55.01%) was statistically significant when compared to normals (-3.05%, sd 41.46%, $p = .002$) and migraineurs (-6%, sd 58.99, $p = .006$). There was no significant difference between other patient groups, including unilateral vestibular neuritis ($p = .610$), BPPV ($p = .824$), Ménière's disease ($p = .605$), Migraine ($p = 1$) and normal controls.

Table 3.2 Utricular Asymmetry (Mean $\pm$ sd) in different patient groups in tabular format.

	N	UVN	BPPV	MD	Migraine	BVH
Mean Utricular Asymmetry (%)	-3.05	22	16.3	22.1	-6	69.57
sd utricular Asymmetry (%)	41.46	35.52	48.94	47.42	58.99	55.05
sem utricular Asymmetry (%)	5.54	11.23	15.48	15	14.75	20.81
Mean canal paresis (%)	n/a	17.6	n/a	39.5	n/a	38.71
sd Canal paresis (%)	n/a	18.34	n/a	28.1	n/a	33.48

3.3c Further details in different patient groups

The following describes further details of measures of vestibular function in the different patient groups.

Chronic vestibular neuritis group: detailed results

10 patients with acute vestibular neuritis were followed up and utricular function performed during chronic stage of the disease (> 6 months). The age range was 35-78 years (mean 51.8 years sd 15.67 years). There were 7 females and 3 males. 5 patients were affected on the right side and other half on the left side.

Note: 5 subjects with Right UVN and 5 subjects with Left UVN. Positive canal paresis and positive utricular asymmetry denote left sided weakness on the test. Also note 2 patients with R sided UVN but mild Left canal paresis.

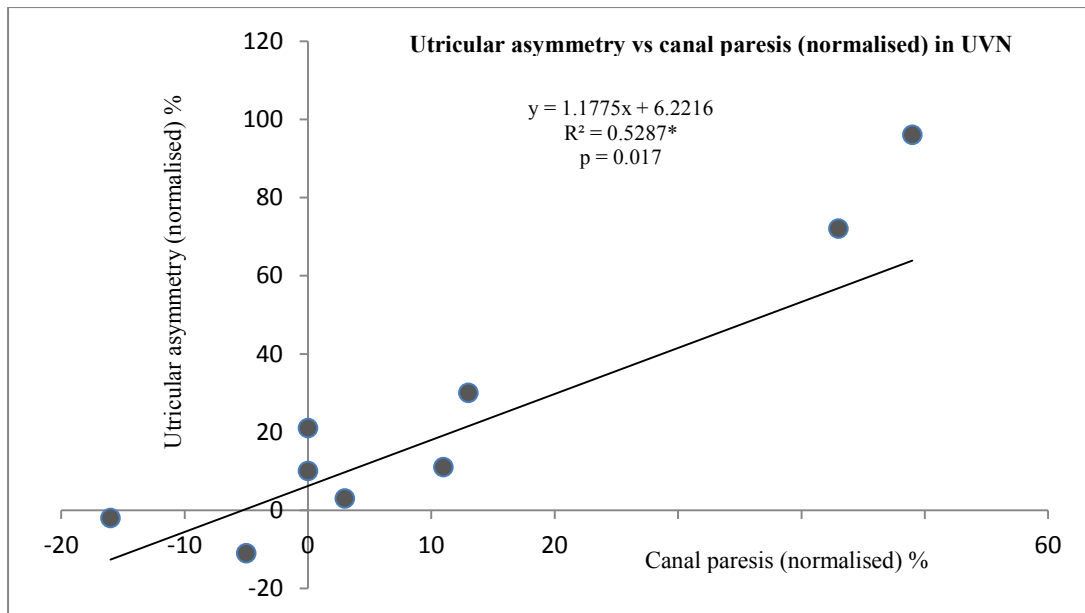


Fig 3.4 shows correlation between utricular asymmetry vs canal paresis in chronic UVN.

The above figure shows that if the canal paresis is significant in chronic unilateral vestibular neuritis then we have a good chance of having same sided utricular asymmetry by approximately 52%. Furthermore, it also shows that there are chronic vestibular neuritis patients who do not have near normal resolution of canal function or utricular function. However, this is not reflected in their subjective symptoms as the 3 patients who had significant canal paresis even after 6 months had low numbers on Dizziness Handicap Inventory total scores (12, 8, 8 respectively). Also, there was no overall correlation of the utricular function with Dizziness Handicap Inventory scores for chronic vestibular neuritis ($r=-0.033$, $p=0.933$ Pearson).

BPPV group: detailed results

Utricular function of 10 patients with posterior canal BPPV (7 right and 3 left) was studied. 5 males and rest females in the age range of 45-85 years (mean 63.4, sd 12.3 years). Utricular function was measured after diagnosis with Dix-Hallpike manoeuvre and again after

canalolith repositioning manoeuvres. It was hypothesised that the repositioning of the otoconia back on to the utricular membrane could affect utricular function.

The normalised utricular asymmetry was not significantly different in utricular weakness before and after canalolith repositioning manoeuvres on paired sample t test. ($p=.588$).

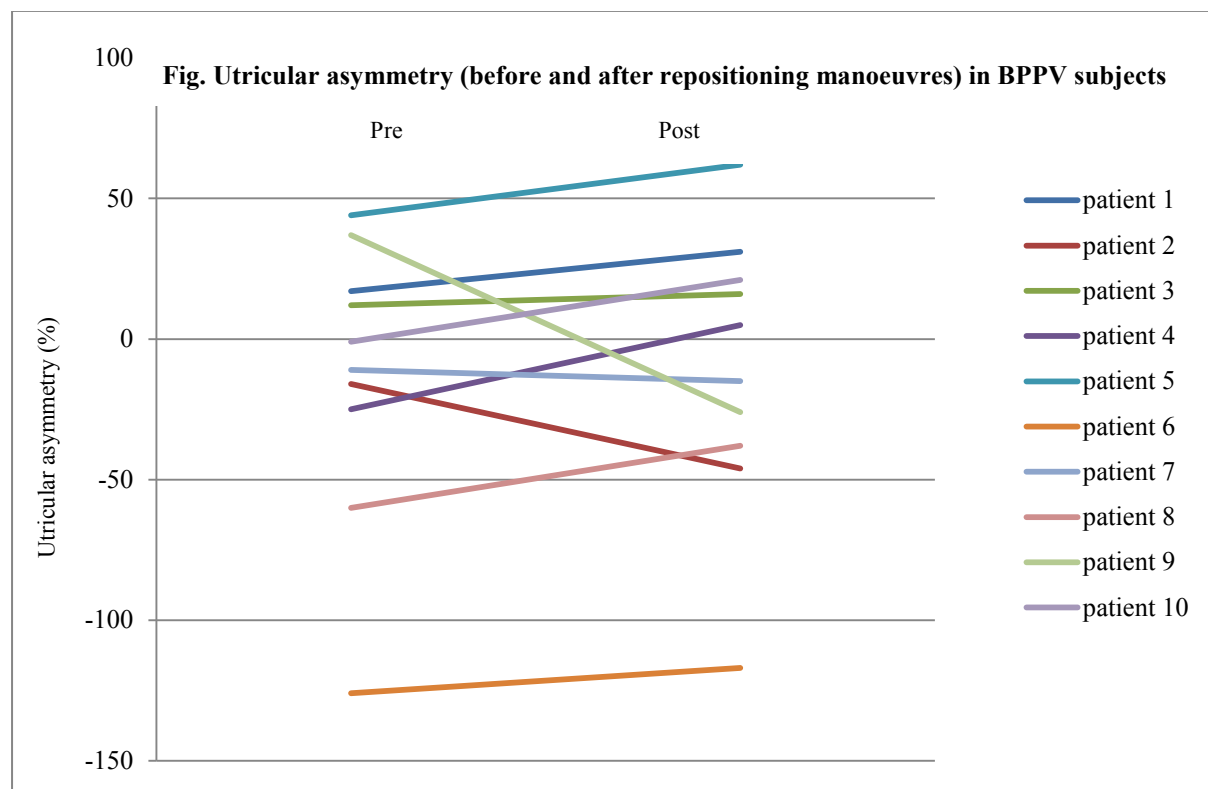


Fig 3.5 Utricular asymmetry (before and after repositioning manoeuvres) in BPPV subjects

Unilateral Ménière's disease group: detailed results

10 patients with unilateral vestibular disease were evaluated for their vestibular function including utricular function testing using unilateral centrifugation paradigm. 5 patients had been affected on the right side and rest on the left side. There were 6 females and 4 males in this study group. The mean hearing loss (Mean PTA, calculated as average of 0.5, 1, 2, 3 kHz) was 33.8-62.5 dB (mean 48.5 sd 9.5dB).

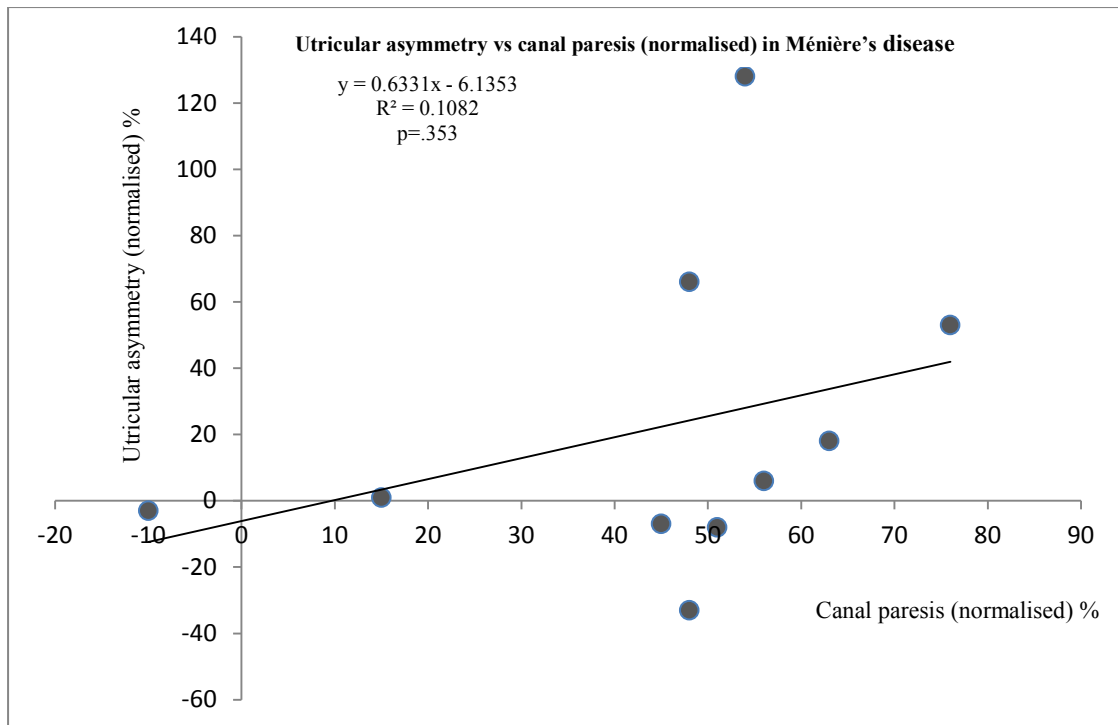


Fig 3.6 shows no correlation between utricular asymmetry vs canal paresis in Ménière's disease.

Canal and utricular function do not correlate well in unilateral Ménière's disease group patients as shown above showing that their dysfunctions can be dissociated within this particular vestibular disorder.

It was somewhat surprising that utricular gain was also found significantly low in unilateral Ménière's disease patients when compared to normals. One way ANOVA between groups was conducted to compare the mean values of the utricular gain of the various groups. There was a statistically significant difference in utricular gain between groups as determined by the one-way ANOVA [$F(5,103)=4.86$, $p = .000$]. Post hoc analysis (Tukey HSD) revealed that the utricular gain was significantly low as expected in bilateral vestibular hypofunction patients (mean utricular gain = 0.25, $sd=0.14$, $p = 0.004$) but also in this group of unilateral Ménière's disease patients (mean utricular gain = 0.39, $sd=0.14$, $p = 0.054$). Utricular gain of other groups was not significantly different from normals. The utricular gain of BPPV (mean

= 0.76, sd= 0.25, p=0.037) was higher than Ménière's disease patients (mean utricular gain = 0.39, sd=0.14) which also reached statistical significance.

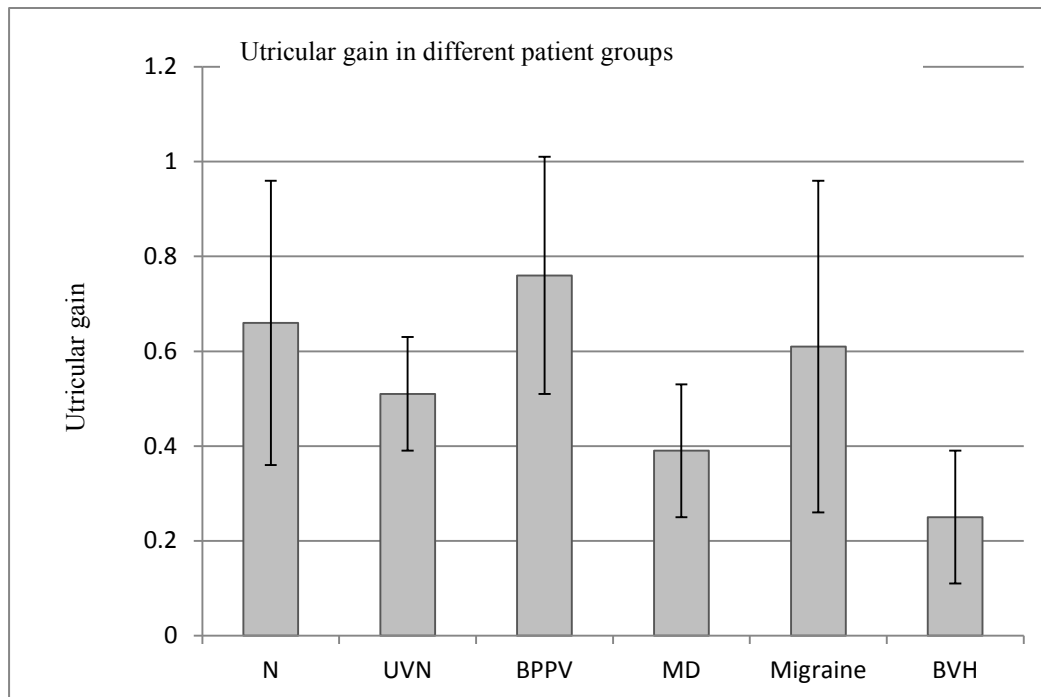


Fig 3.7 Utricular gain in different patient groups

Bilateral vestibular hypofunction group: detailed results

There were 4 male and 3 female patients in the age range of 24 to 78 years in this group. The diagnosis was based on the total canal response <20 deg/sec, these patients demonstrated significantly very low gain (mean $0.25 \pm$ sd 0.14)- described above. With such low gains, the utricular asymmetry values are unreliable. Hearing was normal in most cases except in one lady who had H.influenzae meningitis and suffered sudden hearing loss.

Vestibular Migraine group: detailed results

Fig 3.8 shows the static and dynamic SVV values of the migraineurs of our study. All 16 patients (5 M, 11F) did not show any abnormality in utricular function (utricular asymmetry = -6% sd 58.9) and utricular gain (0.606, sd 0.353). 11 patients in this group underwent

bithermal caloric tests which was normal (canal paresis asymmetry = -5.3, sd 16.3). 7 patients had full ENG testing and 5 were found to have normal ENGs. 1 had suboptimal recording due to sleep and other showed 25% directional preponderance on gain and 8% directional preponderance on time.

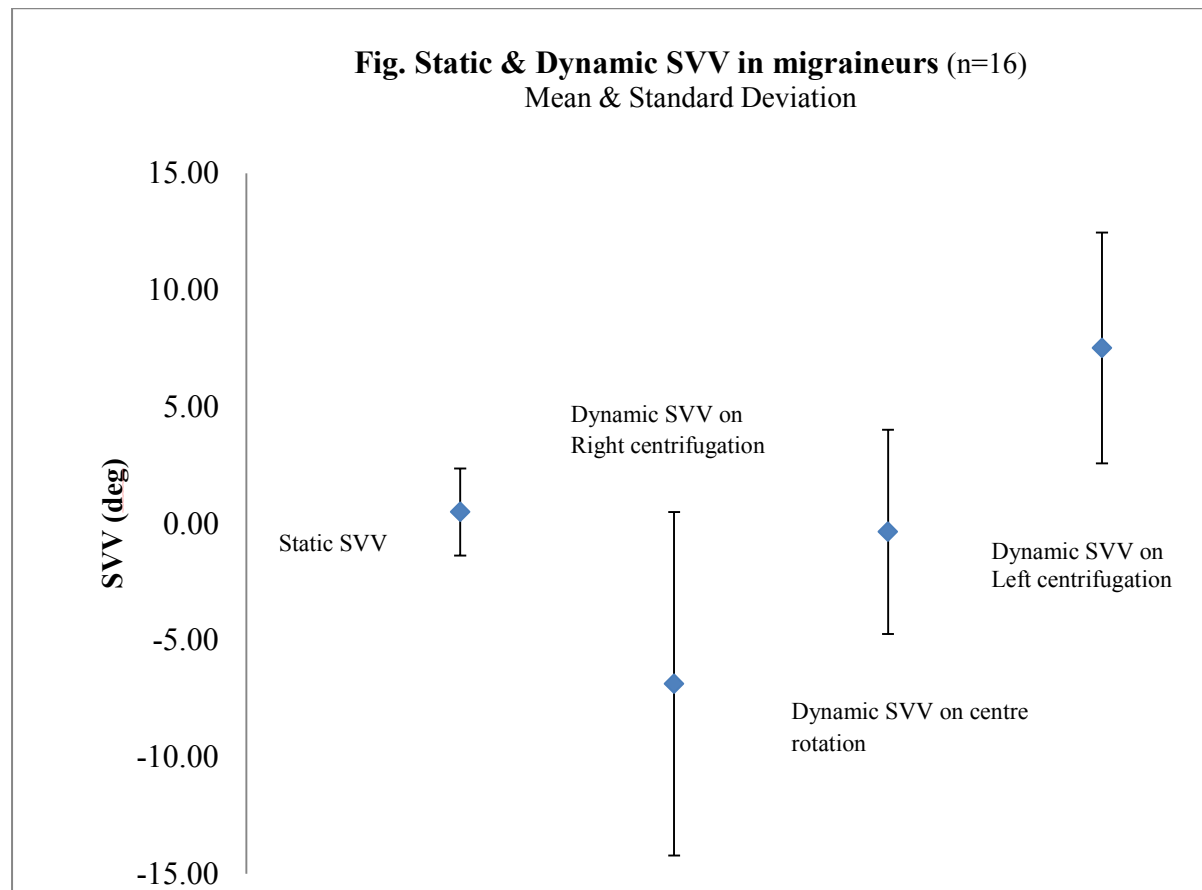


Fig 3.8. **Static & Dynamic SVV in migraineurs (n=16)** (Mean & Standard Deviation)

3.4 Discussion

This work is partly aimed at validating the technique of unilateral centrifugation and gain some insight in the range of expected utricular abnormalities present in the general neurological, clinical scenario. The above results demonstrate the measurement of dynamic utricular function in normal controls and in patients with various common vestibular disorders. Dynamic utricular function is preserved in most of our patient groups including

chronic vestibular neuritis, BPPV, unilateral Ménière's disease and migraineurs. Patients with bilateral vestibular hypofunction show impaired utricular function as revealed by significantly low utricular gain. This is comparable to their overall decrease in canal function (total canal response < 20 deg/sec). In unilateral centrifugation technique, the SVV responses are otolithic (predominantly utricular) as the rotating chair translates, thus exposing the utricles to centrifugal forces, after the canal responses have subsided.

Chronic unilateral vestibular neuritis (> 6 months) group (UVN): discussion

It is common to find some degree of loss of utricular function in the acute phase of vestibular neuritis. This has been shown with static measurements of SVV in the first few days of the onset of the acute vertigo (Min KK et al, 2007), dynamic SVV testing using unilateral centrifugation technique (Hong SM et al, 2010) or measuring utricular function using oVEMPs (Manzari et al, 2011). This acute loss of utricular function is explained by the natural history of the disease as the superior vestibular nerve either alone or together with inferior division is most commonly affected (Kim and Kim, 2012; Magliulo et al, 2014). Superior vestibular nerve supplies horizontal canal, anterior canal and utricle. However, what we were interested in was to find out if this acute loss still persists after 6 months of onset of the disease using dynamic centrifugation. And if there is persistent loss of utricular function, can this explain some of the unsteadiness symptoms experienced by these patients even in chronic stages

In our group of 10 chronic vestibular neuritis (diagnosed during acute stages of the disease and followed up to chronic stages) patients, utricular function after 6 months of onset of symptoms was not different from normal controls. Recovery of acute loss of vestibular function using static SVV has been shown (Min et al, 2007; Kim et al, 2008) within 4-6 weeks of retesting using static techniques. In fact, in one study, static otolith function was

found to recover quicker than canal function (Kim et al, 2008). When patients were retested in the subacute stage (i.e., at 6 weeks by Byun et al, 2010) using dynamic testing, significant deviation of dynamic SVV towards the lesion side was present. Recently, Manzari et al, showed complete recovery of utricular function in one patient when followed up prospectively at 3 months. Our study on 10 vestibular neuritis patients show that utricular asymmetry is no longer present when the patients are tested further ahead in their illness, i.e, at 6 months. Also, the utricular asymmetry had no significant correlation with their subjective scores using validated questionnaires (Dizziness Handicap inventory), in agreement with findings showing that complex central visuo-vestibular processes and psychological factors dictate final outcome in vestibular neuritis (Godemann et al, 2005; Cousins et al, 2014).

Interestingly, there were two patients in whom there was incomplete recovery of both canal and utricular function. We were curious to find if their subjective scores were higher than other patients in the same group, but it was not the case. Also, patients with higher DHI scores had normal utricular function. We can conclude that dynamic utricular function returns to normal in most patients in chronic phase of vestibular neuritis and this does not correlate with their subjective symptoms. There was a significant correlation between canal and utricular function in the chronic vestibular neuritis patients which again can be explained on the basis of lesion being most commonly on the superior vestibular nerve.

BPPV group: discussion

It has been well accepted that the debris in the semicircular canal of BPPV patients are otolithic in origin. The direct anatomical connection of the utricle to the semicircular canals makes the debris to be more likely to be utricular.

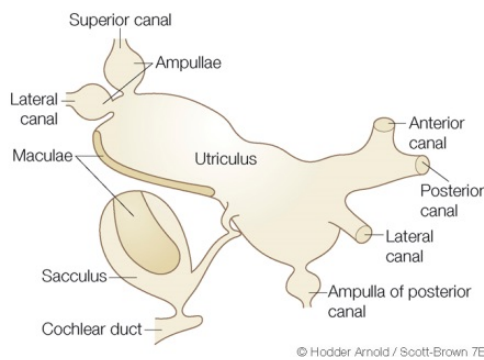


Fig 3.9 showing anatomical interconnections of utricle with the three semicircular canals.

It is expected that the loose otoconial debris fall back from the semicircular canals onto the utricular macula following canalolith repositioning manoeuvres. Following treatment, these patients complain of initial general unsteadiness lasting few days (von Brevern et al 2006, Seok et al, 2008) which could be due to falling back of the debris onto the utricular macula. We were interested to document changes in dynamic utricular function following canalolith repositioning manoeuvres in this group of posterior canal BPPV patients. Utricular function was tested after diagnosis of BPPV and then retested immediately after the canalolith repositioning manoeuvres.

10 patients with posterior canal BPPV did not show any utricular asymmetry when compared with normal controls using unilateral centrifugation technique. On repeat testing immediately after the canalolith repositioning manoeuvres, there was no significant change in the utricular asymmetry. These results are in agreement with no change in amplitude on oVEMPs data immediately after treatment (Bremova et al, 2013) although VEMP pathways, with characteristic short latency (few ms), are likely to be different to the results of our unilateral centrifugation test deployed over many seconds. oVEMPs and unilateral centrifugation are evolving fields in vestibular medicine. For the sake of clarity, a brief description of how the stimulus for oVEMPs was generated has been described. The stimulus used in this study for eliciting otolith responses are bone conducted generated with a mini shaker in the midline of

the hairline, this causes stimulation to spread through mastoid and outward linear stimulation of utricles on both sides. Subsequently, evoked responses in the first 10ms to 20ms from contralateral inferior oblique muscles were measured.

Utricular dysfunction has been demonstrated by measurement of otolith ocular reflex about a week after treatment of BPPV patients by Brevern et al, 2006. More recently, Bremova et al, showed using oVEMPs technique that utricular function is initially normal immediately after treatment in BPPV patients but when tested a week later, becomes abnormal. They proposed that the reattachment of the otoconial debris to utricular macula does not happen immediately but within the first week of successful treatment. Epley (date) had assumed this 'reattachment' when he coined the term 'repositioning' manoeuvres for the treatment of BPPV.

We also had an interesting case where we tested this subject as a normal control and then later on developed BPPV within a month. There was no significant change in utricular asymmetry after development of BPPV or after treatment. Utricular asymmetry values were 29%, -1%, 21% during normal, after diagnosis of BPPV and immediately after treatment of BPPV respectively. However, this could be interpreted as if, for this person, values of 21-29% asymmetry are his norm and that the change to -1% represents an abnormal value. Unfortunately we have not been able to re-examine this subject.

Unilateral Ménière's disease group : discussion

Kumagami et al reported decreased utricular function using static SVV during acute Ménière's disease attacks. Conversely, Manzari et al, 2010 has reported increase in utricular function using oVEMPs during acute attack of Ménière's disease when compared to quiescent phase. They argue that there is dissociation between static and dynamic utricular function (measured using during acute attack of Ménière's disease which is similar to

dissociation between static and dynamic horizontal canal function (Funabiki et al, 1999; Maire and van Melle, 2008). We argue abnormal static SVV cannot be fully explained by only utricular dysfunction as proposed by Kumagami et al, 2009. The static SVV tilt is not specific to otolith function and contribution of the vertical canal ocular pathway to cause ocular torsion has been well documented (Jauregui-Renaud et al., 2001; Pavlou et al., 2003.)

We did not find any significant utricular asymmetry in our group of unilateral Ménière's disease patients by measuring dynamic SVV using unilateral centrifugation profiles. The patients were not tested during an acute phase of vertigo and therefore our results are comparable to pretreatment testing of dynamic SVV in Ménière's disease patients by Helling et al (Helling et al, 2007). The gain in these patients with unilateral Ménière's disease was found to be on the lower side, suggesting the possibility of subclinical bilateral vestibular hypofunction.

Vestibular migraine group:discussion

There is a considerable overlap of symptoms between Ménière's disease and vestibular migraine and we were interested to investigate and compare the dynamic utricular function in these two groups of neurotology patients. Utricular asymmetry in both these groups was not significantly different from normal controls. Various reports have been published regarding some form of peripheral vestibular deficits in migrainous patients (Lee et al, 2000; Celebisoy et al, 2008; Casani et al, 2009). Recently, similar abnormalities on oVemps and cVemps have been recorded both in Ménière's disease and migraine (Zuniga et al, 2012). In our group of Ménière's disease and Migraine patients we did not find any abnormality in utricular asymmetry using unilateral centrifugation techniques. The differences observed between our data and other studies may relate to 'true' biological differences, e.g. short latency pathways subserved by VEMPs may reflect recruitment of irregular, more dynamic vestibular units

rather than longer acting, presumably regular vestibular units, stimulated by our centrifugation technique (Goldberg and Fernandez, 1976). However, technical issues such as different sizes in the normal control groups or statistical approach may be responsible for the different conclusions.

3.5 Conclusions

We found that unilateral centrifugation technique for testing utricular function is safe and straightforward to perform with good patient acceptability and is technologically sound. It provides potentially useful complementary information about unilateral utricular function of the inner ear. The technique is validated by the finding that the bilateral vestibular hypofunction group had significantly low gain.

A particular use of the test is also to assess vestibular function in operated ears with grommets in situ where standard tests like bithermal caloric test are contraindicated or the newer tests like air conducted VEMPS can produce unreliable results due to hearing loss. Recently, a case report of sudden and unrecovered hearing loss post VEMPs procedure due to acoustic trauma has been reported (Mattingly et al, 2015). Finally, different areas of the vestibular systems can be affected and one test may not reveal abnormalities while the other might do. The migraine group was included as often overlapping symptoms are present with Ménière's disease and we are still looking for discriminatory test between the two.

Chapter 4

A study of utricular function in Ménière's disease

4.1 Introduction

In 1861, Prosper Ménière' first presented his landmark paper on vertigo “*Me'moire sur des le'sions de l'oreille interne donnant lieu a`des sympto`mes de congestion ce're'brale apoplectiforme*” before the French Academy of Medicine (Baloh, 2001). He described cases of episodic vertigo and hearing loss and controversially pointed out for the first time that the location of these events was in the inner ear and not in the brain. He had found normal brain and spinal cord but bloody exudate in semicircular canals of inner ear on autopsy in a little girl who had complained of acute vertigo and deafness. Although he did not describe the classical disease himself but nevertheless, it carries his name (Baloh, 2001).

Ménière's disease is a clinical disorder defined as the idiopathic syndrome of endolymphatic hydrops (American Academy of Otolaryngology-Head and Neck Surgery committee, 1995). And the presence of the syndrome of endolymphatic hydrops is clinically characterised by recurrent and spontaneous attacks of vertigo, hearing loss, aural fullness and tinnitus. The introductory remarks of the above committee (in 1972) were ‘Ménière's disease is capricious in both in its behaviour and response to treatment’ which explicitly summarises the challenges faced by the patients and the clinicians up to date.

Briefly, the vertigo attacks in Ménière's disease are characteristically episodic and spontaneous with each episode lasting from 20 minutes to several hours. The attacks are debilitating and associated typically with nausea and commonly vomiting with a phase of disequilibrium following the episodes for few days. Also, the attacks are spontaneous and unpredictable causing great anxiety and stress and making Ménière's disease a difficult

chronic disease to deal with (Van Crujisen N, 2003). Furthermore, the disease can become bilateral in approximately one third of the patient population (Thomas K, 1971).

In addition to the typical episodic vertigo attacks described above, there are a small percentage of patients who may experience sudden drop attacks, or ‘Tumarkin’ attacks. These attacks are of vestibular origin but not arising from canals. In 1936, Tumarkin himself described these fatal falls in Ménière’s disease patients as ‘otolithic apoplexy’ rather than of episodes of canal origin (Tumarkin, 1936). The falls are characteristically described to be of instantaneous onset without any premonition or neurological phenomenon and with immediate recovery within less than a minute. The attacks are perceived as being suddenly pushed to the ground or to one side with characteristic absence of syncopal features (Odkvist and Bergenius, 1988). More recently, the drop attacks have been noted with inner ear disorders not characteristic of Ménière’s disease and responding reliably well to ablative vestibular procedures on long term follow up when other treatment methods have failed (Ishiyama et al, 2001). Interestingly, such frank otolith/ utricular phenomenon including crisis and subsequent invasive and ablative treatments have been described but still there are major gaps in the understanding of the utricular function itself. The study of otolith function has been only possible recently with advancement in evoked moogenic potentials on one hand and rotational techniques on other. The otolithic crises as described by Tumarkin in Ménière’s disease patients as well as the drop attacks in other inner ear disorders is based on speculation without any evidence concerning the otolith function in these patients. It is interesting that these drop attacks responded to ablative surgery like vestibular nerve section or labyrinthectomy, even in older patients (Ishiyama et al, 2001).

The aim of this research study was to specifically study the utricular function in patients with unilateral Ménière’s disease using the unilateral centrifugation paradigm described in the previous chapters. One reason for doing this is that, of all aspects of inner ear function,

utricular function is the least known given the technical difficulties present in delivering a physiological stimulus to the utricular macula. Once we establish if there are significant abnormalities in utricular function, we will aim to correlate its function with that of conventional tests of inner ear function (e.g. caloric tests, audiogram). In turn this comparison will allow us to estimate if the putative utricular damage in Ménière's disease could be indirectly evaluated by simpler, less expensive means (e.g. if Unilateral centrifugation tests results showed an excellent correlation with caloric results and a poor one with audiometry, one could propose that utricular tests are not truly needed in clinical practice as caloric test data would be a good "marker" for utricular function).

4.2 Materials and methods

Utricular function was investigated in 45 patients with unilateral Ménière's disease using the unilateral centrifugation technique. Ménière's disease was diagnosed using the AAO-HNS criteria, 1995. All these patients satisfied the criteria of definite unilateral Ménière's disease. 2 subjects reported sudden spontaneous falls which were presumed to be otolithic in origin. All the subjects performed all the audio vestibular assessments including PTA, speech audiometry, bithermal caloric tests and utricular function experiments in a single test session in random order. The patients were given adequate breaks and they were aware of the right to withdraw from the assessments at any time.

There were 29 cases with left sided Ménière's disease and 16 patients had right sided Ménière's disease. There were 25 female and 20 male participants in the study. The age range varied from 32 – 68 years with mean age of 52.5 (sd 9.9) years. The duration of the symptoms of Ménière's disease varied from 1-20 years (mean 6.3 years, sd 5.1 years). Concurrent neurological disorders like vestibular migraine which can mimic Ménière's

disease were excluded (Radtke et al, 2002). Pregnant women were also excluded as they are not suitable for unilateral centrifugation testing paradigms.

As per committee of hearing and equilibrium 1995 criteria, there were 7 patients with stage 1 MD, 9 with stage 2 MD, 26 with stage 3 MD and 3 with stage 4 MD. The 2 patients who were presumed to be having additional Tumarkin crisis were in stage 1 and stage 3.

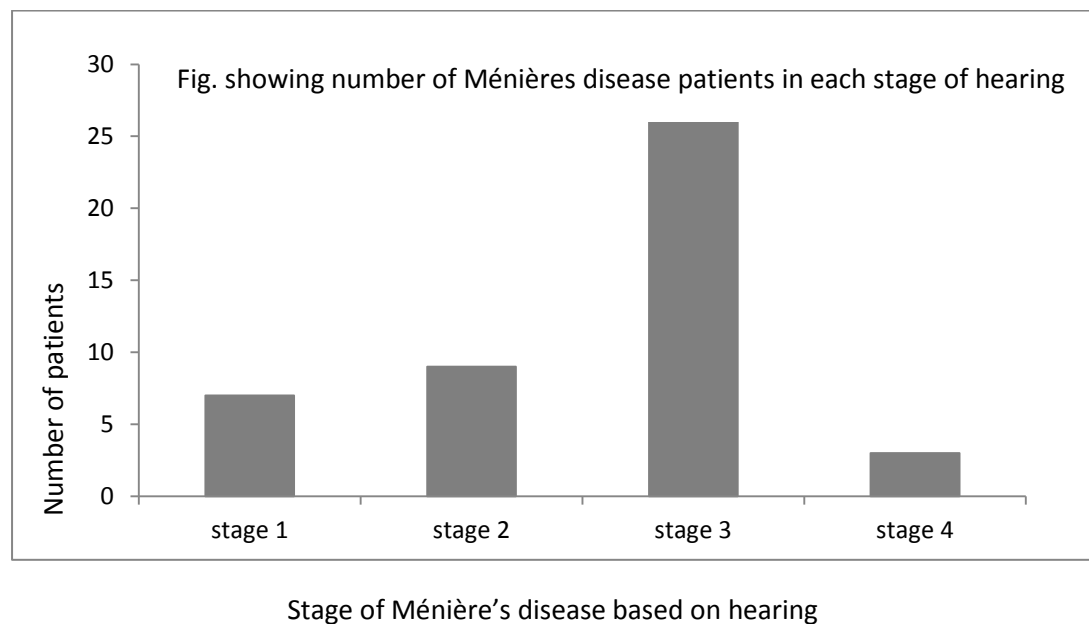


Fig 4.1 number of Ménière's disease patients in each stage of hearing

The normative data for utricular function was derived from the assessment of 47 healthy age matched controls. They were free of any neurotological disorders and voluntarily participated in the study. The age range was between 25-80 years with mean age 49.02 (sd 16.3) years.

4.3 Results

The results are divided into audiological assessment, vestibular assessment, utricular function followed by correlation of these functions for ease of reading.

Audiological assessment:

Pure tone average (average of hearing level in dB at 0.5, 1, 2 and 3 kHz) range was from 3.75 dB-120 dB. Mean pure tone average was 47.22 dB and standard deviation was 20.33 dB. Speech discrimination score varied from 0 – 100% (mean 72.7%, sd 23.9%).

Vestibular assessment:

42 patients underwent bithermal caloric testing. 1 patient had grommet fitted in her affected ear as a treatment for Ménière's disease and 2 other patients did not tolerate the procedure. Taking canal paresis of less than equal to 22% as normal (Cousins et al 2013), 12 patients had no canal paresis and 30 patients had varying degree of canal paresis. The overall mean canal paresis was 36.5% (sd 27.78%). The range was -35% to 76%. There was one patient with significant canal paresis (-35%) on the opposite side and two other patients with significant utricular asymmetry on the opposite side (-78% and -56%).

Audiovestibular function in Ménière's disease patients (n = 45)			
	Mean	sd	Range
Average PTA threshold (dB)	47.22	20.33	3.75 to120
Speech score (%)	72.72	23.85	0 to100
Canal Paresis (%)	36.55	27.88	-35 to 76
Utricular Asymmetry (%)	24.14	57.25	-78 to 183
Utricular Gain	0.54	0.24	.16 to 1.28

Table 4.1 showing audiovestibular function in Ménière's disease patient group

Utricular function:

Mean utricular asymmetry on the unilateral utricular centrifugation test was 24.1 % (sd 57.25%). One patient did not tolerate the procedure. An independent samples t test was done to compare the utricular function in patients with unilateral Ménière's disease and in healthy controls. There was a significant difference in the utricular asymmetry between normal (mean = -8.71%, sd 38.42.%) and unilateral Ménière's disease patients (mean = 24.14%, sd

57.25%); $t(90)=3.24$, $p = 0.001$. These results show an increase in utricular asymmetry in patients affected with unilateral Ménière's disease when compared with normal controls.

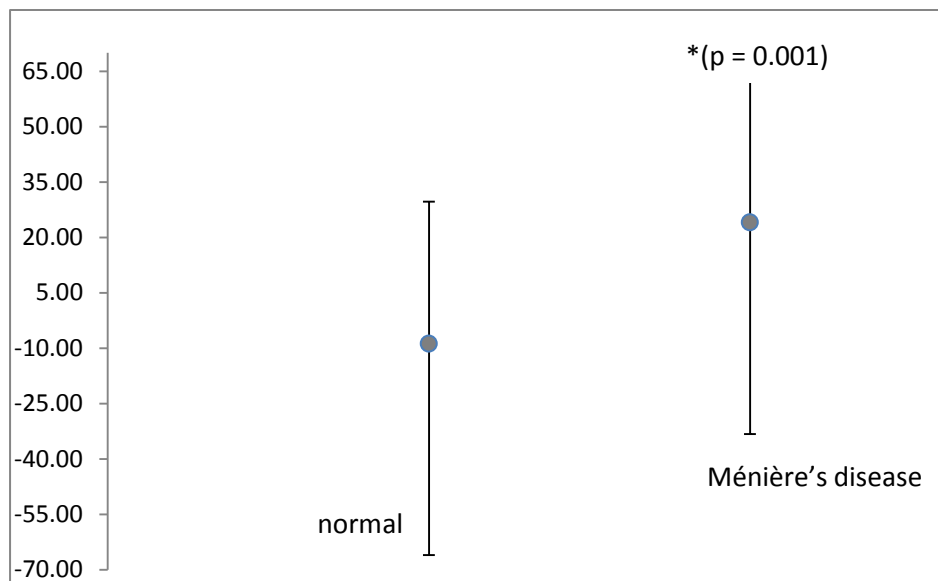


Fig 4.2 Utricular asymmetry in normal vs Ménière's disease group

Utricular gain in unilateral Ménière's disease patients: Similarly, there was significant difference in utricular gain in normal (0.65, sd 0.31) and in patients with unilateral Ménière's disease (0.54, sd 0.24); $t(90) = 2.05$, $p=0.04$. The results suggest that utricular gain in unilateral Ménière's disease patients was reduced compared to normal controls.

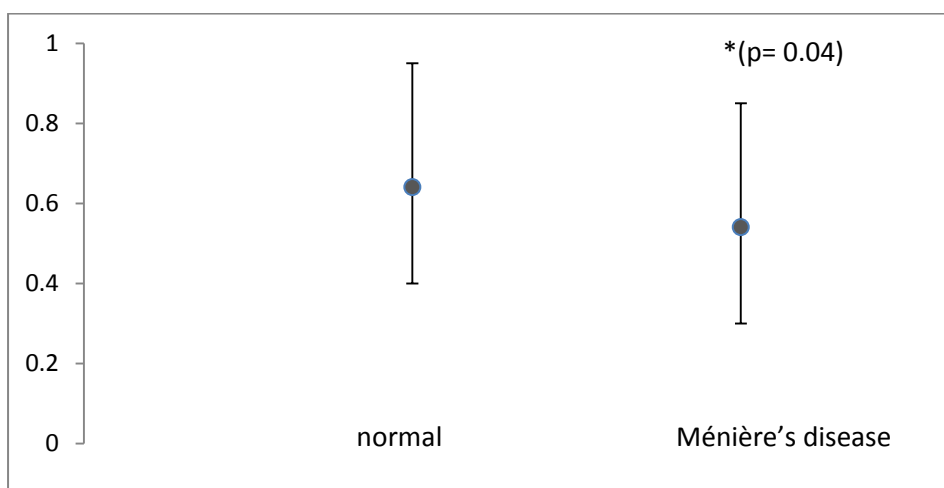


Fig 4.3 Utricular gain in normal vs Ménière's disease group

The two patients who suffered from clinical otolith dysfunction also underwent utricular function testing. Unfortunately, one of them did not tolerate the experiment and the other subject had normal utricular function (utricular asymmetry 8%, utricular gain 0.54). The subject who completed the experiment was in stage 3.

4.3a Correlation of audiovestibular function in Ménière's disease

We decided to correlate the various measures of inner ear function for investigating hydropic changes in Ménière's affected ears in our patients. Firstly, hearing function was correlated with canal and utricular function. Secondly, the two measures of vestibular function and hearing function were correlated with each other.

Canal vs hearing function:

There was a significant relationship between hearing loss and canal paresis in our study group (Pearson's $r = 0.498$, $p = 0.001$). $n = 42$.

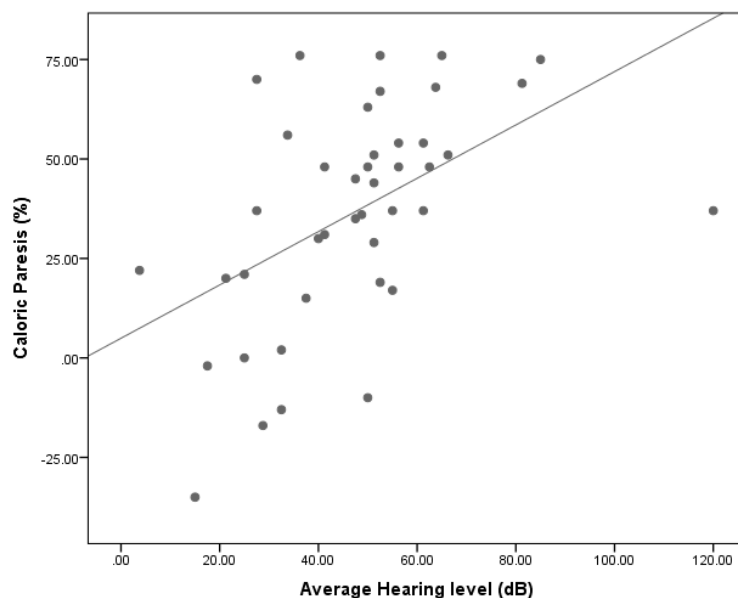


Fig 4.4 showing correlation of canal function and hearing loss in Ménière's disease group (please note caloric paresis on the figure refers to canal function)

Utricular vs hearing function:

Hearing loss was well correlated with utricular function in this group of patients (n=44), Pearson's $r = 0.526$, $p = 0.000$. . There was no significant correlation between utricular gain and hearing loss (Pearson's $r=0.009$, $p=0.952$)

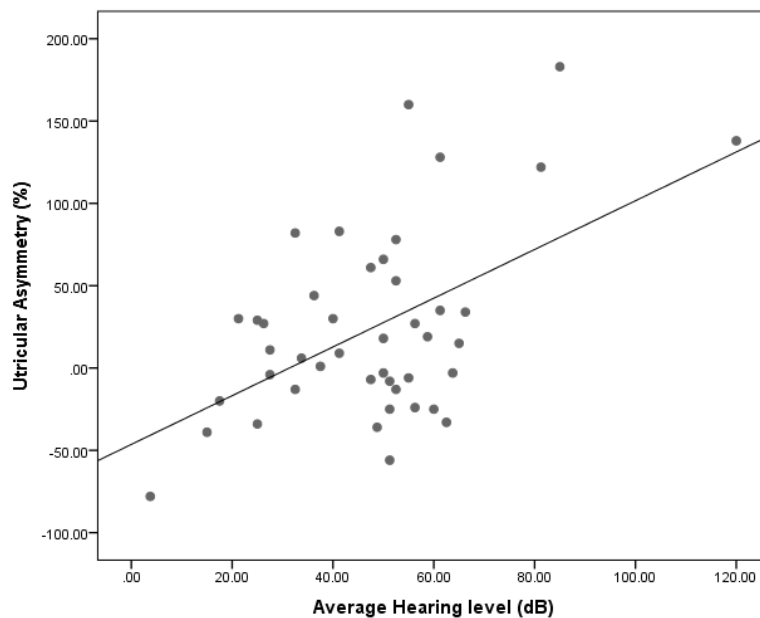


Fig 4.5 showing correlation between utricular function and hearing loss in Ménière's disease group

Canal vs utricular function:

We were interested to discover if the two measures of vestibular function in this study group revealed any correlation or not. This was not found to be significant (Pearson's $r = 0.217$, $p = 0.173$).

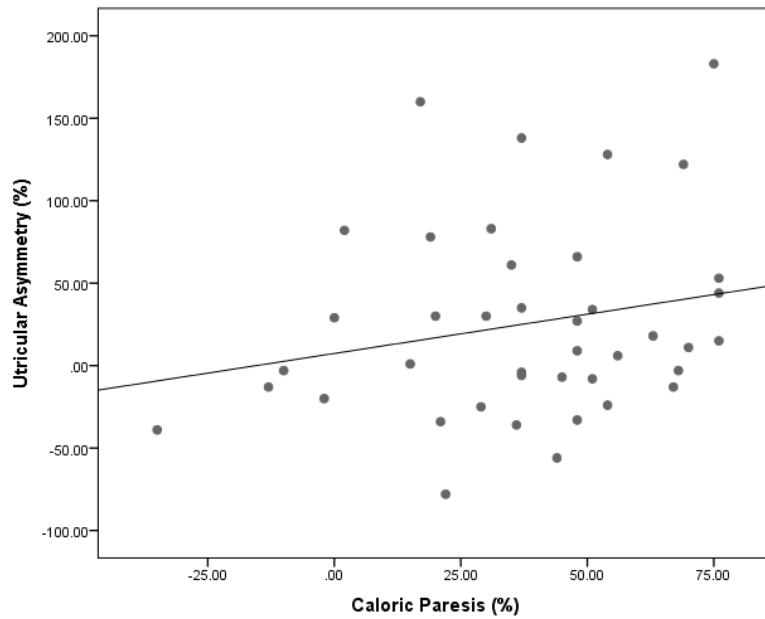


Fig 4.6 showing correlation between utricular asymmetry and caloric paresis in Ménière's disease group. (please note caloric paresis on the figure refers to canal function)

Hearing level vs speech score:

As expected, there was a clear negative correlation between these two variables. (Pearson's $r = -.758$, $p = 0.000$).

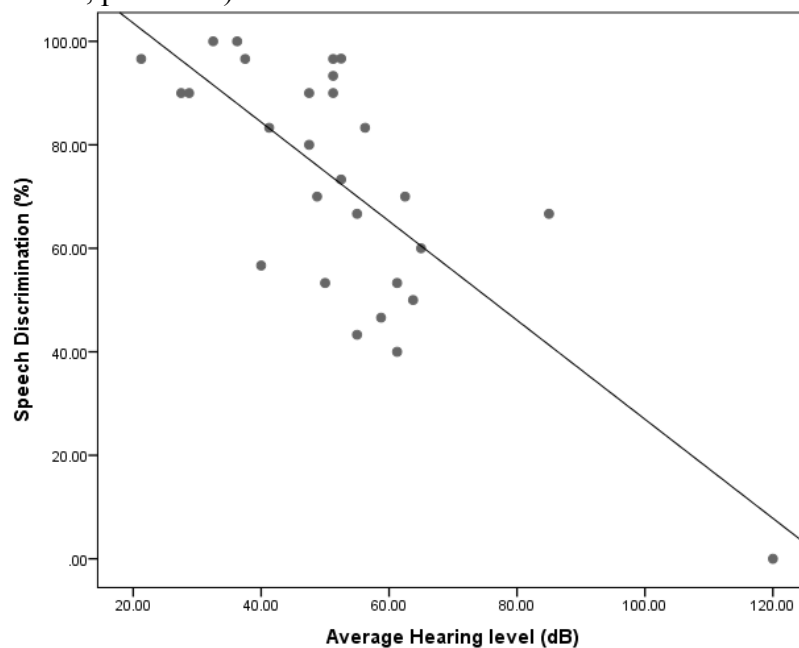


Fig 4.7 showing correlation between speech discrimination and hearing loss in Ménière's disease group

Further analysis with multiple linear regression analysis showed that hearing loss and interestingly being female was a predictor of higher utricular asymmetry. $F = 6.1$, $df (2/22)$, adjusted R square = 0.3, $p = 0.008$. However, utricular asymmetry did not vary with stage of hearing loss in this group. This means we cannot say that the worse the hearing loss, the worse the utricular loss will be.

4.4 Discussion

Utricular function using unilateral centrifugation technique was studied in 45 patients with unilateral Ménière's disease. The purpose of this study was to investigate utricular function in patients with Ménière's disease and to determine its relationship with other measures of audiovestibular function.

We found that overall utricular function is reduced in unilateral Ménière's disease patients. There is increase in utricular asymmetry and reduction in utricular gain when compared with normal subjects of similar age group. 13 out of 45 patients (28.8%) had significant utricular asymmetry (normal utricular asymmetry taken as $\pm 50\%$).

Our results are similar to the study of utricular function of a smaller group of Ménière's disease patients refractory to conservative treatment (Helling et al, 2007). In this study, utricular function was assessed before and after intratympanic gentamicin using unilateral centrifugation technique. The protocol for rotational testing was similar to our study with chair velocity of $300^\circ/s$ and chair displacement of 3.5cm (cf. chair velocity $400^\circ/s$ and displacement 4.2cm) The pretreatment utricular function is comparative to our sample as 6 out of 19 (32%) underestimated the tilt of SVV in their group of Ménière's disease patients.

With recent technological advances in both rotational testing and evoked potential testing, there has been a surge of interest in measurement of otolith function in different vestibular

problems. Utricular function has been measured with both using oVEMP test and unilateral centrifugation. Studies investigating utricular function with oVEMPs testing in unilateral Ménière's disease also found that utricle is affected in a quarter of their cases (Huang et al, 2011) which is similar what we found in our unilateral Ménière's disease study population (28.8%). Utricular stimulation was generated via an electro-mechanical hand held vibrator just above the glabella and myogenic responses measured from lower eyelid. Interestingly, only unilateral Ménière's disease patients were included in our study as well as above mentioned studies making patient population closely comparable. However, the tests are intrinsically different, bone conducted vibration of oVEMP testing is a high frequency stimulus similar to high frequency head impulse testing (Curthoys 2006). The Unilateral centrifugation is a rotational test and the stimulus will be more likely to be low frequency continuous stimulation. So we cannot say if the quarter of patients with utricular abnormality in our sample would overlap completely with those results reported with the oVEMP test. As far as we know this question is unanswered as no published studies are available comparing oVEMPs and unilateral centrifugation test results. In addition, it should be noted that we have investigated more than double the number of patients compared to above studies (Huang et al, 2011, n =20; Helling et al, 2007, n = 19).

It was also interesting to compare the other measures of inner ear function with utricular function, for instance in case a simple and inexpensive test as a conventional audiogram could become a surrogate marker for utricular function. Sensorineural hearing loss is one of the main diagnostic criterion for unilateral Ménière's disease and determines the staging of the disease as per the committee guidelines. Hearing function was found to be affected in varying degrees among our patients (stage 1 – 15.56%; stage 2 – 20%; stage 3 – 57.7% and stage 4 – 6.67%). In our study, both canal paresis and utricular asymmetry correlated well with hearing loss but not with each other. This might indicate varying degrees of hydropic

changes in different parts of labyrinth the disease ear. Also, it is speculated that hydropic changes of the cochlea are followed by saccule. Utricule and canals are usually affected at the later stages of the disease. It also means, unfortunately, that neither caloric or audiometry on their own are good substitutes for the unilateral centrifugation test. Utricular gain did not correlate with hearing loss but this can be explained that hearing loss is for unilateral affected ear and utricular gain is assessment of overall utricular system so in principle two different parameters.

Extensive comprehensive review of histopathological studies of 650 temporal bones including 163 cases of Ménière's disease (identified using 1995 criteria) have finally concluded that endolymphatic hydrops is the cause of Ménière's disease. It also noted that endolymphatic hydrops is much more common than Ménière's disease and the exact set of pathophysiological events leading up to clinical presentation in symptomatic patients have not been found (Foster and Breeze, 2013). MRI studies using local contrast into the ear with intratympanic gadolinium injections also have demonstrated distension of membranous labyrinth in Ménière's disease patients (Fiorino and Pizzini, 2011).

Utricular macula of four Ménière's patients who underwent labyrinthectomy was studied by Rosenhall et al, 1977 postoperatively. They found that utricular macula despite severe symptomatic Ménière's disease necessitating labyrinthectomy had minor ultrastructural alterations. Vacuolation of sensory cytoplasm and cystic separation of type 1 sensory cells and their nerve chalices were suggestive of degeneration which could be attributed to Ménière's disease.

There are clearly areas of gaps in understanding of differential involvement of the labyrinth by the hydropic process in Ménière's disease and hence understanding of the utricular function in comparison with histopathology is more than just interesting.

Chapter 5

A comparison of symptoms with utricular function in Ménière's disease

5.1 Introduction

Ménière's disease is predominantly a clinical diagnosis on the basis of a characteristic symptom complex with an evidence of hearing loss and normal brain imaging. The typical symptoms are episodes of unpredictable vertigo lasting more than 20 minutes, usually preceded by increase in tinnitus or aural fullness in the affected ear, with or without noticeable changes in hearing. The current consensus on the pathophysiological basis of these disturbances of inner ear function in Ménière's disease is an endolymphatic hydrops. The theory of endolymphatic hydrops has been 'reappraised' recently on the results of intratympanic and intravenous gadolinium enhanced MRI of inner ear (Pykkö et al, 2013) and in the light of extensive histopathological reviews (Foster and Breeze, 2013). Fiorino et al also demonstrated progression of hydrops with increase in involvement of number of sites of labyrinth with duration of disease. Multiple mechanisms including genetic, immune mediated, inflammatory, post viral or trauma have been reported to initiate the hydropic degeneration in the inner ear (Rauch S, 2010). Although what precisely causes hydropic changes in some ears to manifest as Ménière's disease, but not in others, is still unknown.

As noted in the previous chapter, the objective audiovestibular abnormalities can in fact be explained to some extent by hydropic changes. Hydropic changes of pars inferior of the labyrinth (comprised of cochlea and saccule) are more consistent compared to pars superior of the labyrinth (comprised of utricle and semicircular canals) where more differential effects are noted.

Since, by definition, Ménière's disease is a clinical manifestation of endolymphatic hydrops and the diagnostic emphasis is on the characteristic symptoms, the aim of this study is to investigate if the self-reported symptom load is directly comparable with results of end organ testing; especially with the new knowledge of utricular function in Ménière's group. The analysis will help us to determine if the patient's 'perception' of his the symptoms correlates, or not, with measurements of the the audiovestibular function of the damaged ear. This comparison is opportune because recent technological advances have now made it possible to study the utricular function in more detail which allows us to make more comprehensive evaluation of the symptoms vs inner ear function.

There are numerous reports on how symptoms of Ménière's disease affect quality of life and emotional wellbeing (Cohen et al, 1995, Kirby and Yardley, 2012). The aim of management in most clinics is however, symptom control and preservation of inner ear function, so understanding of the correlation between the two (subjective and objective measures) will help the understanding of the 'capricious' disease and its management plan. Specifically, during management, the direction of therapy can be based on whether to address the otolith related abnormalities or canal related dysfunction, or both, or neither of them. However, although optimistic at this stage, it would be hugely helpful if the subjective and objective measures could in some way predict the aftermath of the diagnosis of Ménière's disease, in an individual and thereby guide him/her in the future management of their disorder.

5.2 Material and Methods

Questionnaire data was obtained on a sub set of the main patient group of 45 Ménière's patients. This patient group comprised 35 patients with a diagnosis of unilateral Ménière's disease according to AAO-HNS (1995) criteria gave their written, informed consent to the study which was approved by the ethics committee . The mean age of the patient population

was 53.2 (sd 9.8) years with range varying from 32-68 years. There were 21 female and 14 male participants in the study. The duration of disease was from 1-20 years (with mean duration of 7.2 years (sd 5.5 years)). There were 11 right sided Ménière's disease participants and 24 left sided Ménière's disease participants. The main exclusion criteria were pregnancy due to contraindication of testing the patient with unilateral centrifugation paradigm and a concurrent history of vestibular migraine which could be a potentially significant confounding factor (Ratke et al, 2002).

Questionnaires:

Patients reported their symptoms by completing validated questionnaires (i – iv below) for comparison with audio-vestibular test results (Chapter 4). Please find the questionnaires in the appendices section (I-IV).

The symptom load and functional status were self-reported by the patient population using different validated questionnaires and stating the number of attacks in the preceding months.

A. To assess symptom load and ongoing disease activity:

- i) Vertigo symptom scale (short form) by Yardley et al, 1992, a symptom specific questionnaire which measures the severity of vertigo and somatic anxiety in the last month. The short form has 15 items and eight of them enquire about vertigo and balance symptoms. The remaining 7 items are related to autonomic anxiety symptoms. Each item is scored between 0-4 and scores above 12 are regarded as severe (Yardley et al, 2004). The short form has shown good internal consistency and moderate test-retest reliability (Yardley et al, 1998). The questionnaires have been repeatedly been used to report dizziness outcome measures in studies involving Ménière's disease patients undergoing treatments (Söderman et al, 2001) or vestibular

rehabilitation (Muller et al, 2015). Please find the questionnaire in appendix III (page 116).

ii) Aural Fullness scale (Garduño-Anaya et al, 2005) – subjective scale. The patients were asked to rate their average aural fullness from a scale of 0-10. It is not a validated scale but has been used in previous studies on Ménière's disease patients (Garduño-Anaya et al, 2005)

iii) Number of vertigo attacks in last six months and the last month-

B. To assess handicapness due to symptoms of Ménière's disease and current functional status:

iv) Dizziness handicap inventory (appendix I- page 114, Jacobson and Newman, 1990)- widely used for self-reporting of functional, emotional and physical impairment due to dizziness. There are 25 items with a response of no, sometimes or yes. Higher the score, worse is the self-perceived handicapness due to dizziness. Garduno-Anaya et al, 2005 had used to report outcomes of intratympanic treatment in refractory Ménière's disease patients.

v) Tinnitus handicap inventory (appendix II- page 115, Newman, 1996)- universally used tinnitus questionnaire for symptom assessment and to report treatment outcomes. This 25 item tinnitus questionnaire to report self perceived tinnitus severity. There are 11 items to assess functional limitations, 9 items to assess emotional impact and remaining five items assess catastrophic responses to tinnitus. For example, the catastrophic item would be 'do you feel you no longer cope with your tinnitus?' The response for each item is either yes, sometimes or no. Higher the score, more severe the tinnitus handica is for the individual. It has excellent internal consistency and reliability (Cronbach's alpha = 0.93). THI has been used in several studies

with Ménière's disease patients (Kinney et al, 1997; Garduño-Anaya et al, 2005; Herriaz et al, 2006).

- vi) Functional level scale as per AAO-HNS, 1995 criteria. Please see appendix IV- page117.

Statistical methods:

After initial analysis of symptom load, relationships between audiovestibular test results and questionnaires were investigated firstly by Pearson correlation and the significant correlations at or below .01 level were included. The full correlation matrix is omitted because of size and lack of many significant relationships. But for linear regression and factor analysis p values of <0.05 were considered significant. Negative values were used when asymmetry was on unaffected side.

Subsequently, Factor analysis (principal orthogonal components with varimax rotation implemented in IBM SPSSTM) was performed on the audiovestibular test results and a subset of the more important questionnaires to determine underlying structures to the data set.

5.3 Results

5.3a Results of Questionnaires

- i) Vertigo symptom scale (short form)- Vertigo symptom scale (short form) is a 15 item questionnaire. It retrospectively assesses symptom load over the last month and scores can range from 0-60. The mean score for our patient group was 20 (sd 10) clearly suggestive of severe dizziness (severe dizziness has been defined as ≥ 12 on total scores) as suggested by Yardley et al, 2004.

As these patients were being assessed with multiple questionnaires and audiovestibular function tests in one session, it was important to keep the overall time length of assessments at a reasonable level for the participant accordingly. The short form was chosen, following discussion with Dr Lucy Yardley, as a reliable measure of vertigo symptoms before and after treatment of the Ménière's disease patients. Some of these patients also voluntarily participated in the ongoing randomised controlled trial comparing the two most commonly used transtympanic treatments for unilateral, refractory Ménière's disease.

ii) Aural fullness scale is a subjective scale on which patients were asked to give the average score rather than on the day score. The mean of the average score of aural fullness of our Ménière's study group was 5.2 (sd 3.1). This reflects significant average aural fullness in this group.

iii) Number of vertigo attacks: The participants were asked retrospectively about the number of vertigo attacks lasting more than 20 minutes in the last 6 months and in the last month. 27 patients could reliably recollect the number of vertigo attacks and hence only these were included. The mean numbers of vertigo attacks in last 6 months were 17 (sd 17) attacks, ranging from 2-65 attacks. And the mean number of vertigo attacks in the last month 5(sd 6), range 0-25. There was good correlation between the two measures (pearson's $r = 0.78$, $p < 0.000$). One would assume that if there are significant numbers of vertigo attacks, the disease would be fairly active, whether it reflects on functional status of an individual or not. But for research purposes, the delineation between active and inactive phase would be having significant numbers of attacks. This is important as Ménière's disease is a chronic disease with phases of relapse and remission and we wanted to assess end organ function during relapses.

iv) Dizziness Handicap inventory (Jacobson & Newman)- The total scores varied from 16-86 on this scale suggesting mild activity limitation and participation restriction to severe activity limitation and participation restriction (Jacobson and McCalsin 2003). The mean score was 52 (SD 18) suggesting moderate to severe handicapness due to dizziness symptoms of Ménière's disease (Kinney, Sandridge and Newman 1997, page 109). Interestingly, age had no effect on dizziness handicap scores but females had higher self reporting of dizziness handicapness (Pearson's $r = 0.395$, $p = 0.019$). This finding is similar to that of Robertson and Ireland, 1995 (total DHI score, $p = 0.02$).

(Note: Jacobson & Newman suggest only total scores after Perez et al 2001 performed Factor analysis on DHI and dizziness characteristics).

v) Tinnitus handicap inventory: the total score varied from 0-96. The mean for our group being 46 (sd 25). Scores above 18 suggest mild limitation of activity and the mean score in our study group suggest moderate limitation.

vi) Functional level scale is a 6 point scale recommended by AAO-HNS for Ménière's disease patients to assess functional impairment. These recommendations are based on the fact measurement of severity of vertigo is subjective and counting number of attacks may not give an accurate account. This is because a few episodes of severe vertigo can be much more disabling than multiple episodes of mild attacks.

The mean score of the functional level scale was 3.457 (sd 0.9) which indicates middle of the scale (1-6). This suggests that most of these patients are significantly impaired by their symptoms, but not to the point of disability. The following table shows the results of different questionnaires and the number of vertigo attacks:

Questionnaire	n	Mean	sd	Range	comments
VSS (short)	35	20	10	1-43	>12=severe
DHI	35	52	18	16-86	
THI	35	46	25	0-96	>18=mild limitation
AFS	35	5.2	3.1	0-10	
FLS	35	3.5	0.9	2-6	
Number of attacks in last 6 months	27	17	17	2-65	
Number of attacks in the last month	27	5	6	0-25	

Table 5.1 Results of different questionnaires and number of vertigo attacks

Overall, questionnaire data suggest that symptom load of dizziness is severe as assessed by the vertigo symptom scale, moderate to severe handicap on dizziness handicap inventory scores, moderate handicap on tinnitus handicap inventory scores and overall significant impact on their functional levels. Menieres patients also report on average, moderate, aural fullness on the affected side. The average number of more than one attack per week also suggests ongoing disease activity.

Comparison of questionnaires and disease activity:

Vertigo attacks in the last 6 months correlated well with vertigo in Vertigo symptom scale (Pearson's $r = 0.61$, $p = 0.001$) and self-reported poor functional status (Pearson's $r = 0.60$, $p = 0.001$). Vertigo in the last month also correlated well with functional level scale (Pearson's $r = 0.66$, $p = 0.000$) and weakly with vertigo symptom scale (Pearson's $r = 0.42$, $p = 0.032$). VSS correlated with DHI showing internal reliability of the questionnaires (Pearson's $r = 0.55$, $p = 0.001$).

Correlation Coefficient	VSS	DHI	THI	FLS	AFS
Vertigo Symptom Scale (VSS)		.554***		.547***	
Dizziness Handicap Inventory (DHI)			.412***		
Tinnitus Handicap Inventory (THI)					
Functional level Scale (FLS)					.365**
Aural Fullness Scale (AFS)					

Table 5.2 Correlation between different questionnaires (only significant results shown). This shows that if there is significant ongoing vertiginous activity it causes more handicapness due to dizziness ($p=0.000$) and impaired functional status ($p=0.000$). Also there is a significant correlation between handicap due to dizziness and tinnitus ($p=0.007$). And there is also - correlation between functional status and aural fullness ($p=0.015$).

5.3b Comparison of questionnaires with end organ function:

In recapitulation the key feature of the study was to investigate the correlation of loss of audiovestibular function with self-reported symptoms. 24 out of the 35 patients had completed all the questionnaires, self-reporting of vertigo attacks and full audiovestibular testing including utricular function and hence the data was included only from these patients for statistical analysis. Interestingly, none was found on linear regression of what on what???

A significant correlation was found between aural fullness and speech scores which is unexpected suggesting more the aural fullness in the affected ear better the speech discrimination of that side (Pearson's $r = 0.53$, $p = 0.008$). Also noted was a correlation between hearing levels and dizziness handicap inventory scores suggesting worse the hearing in the affected ear, more dizzy the patient is. (Pearson's $r = 0.54$, $p=0.004$).

Factor analysis revealed four components with Eigenvalues >1 which together accounted for 75% of the variance (Table 5.3).

The first component accounting for 25% of variance had very high loadings of DHI and VSS scores and high loading of hearing level indicating a strong association of hearing loss with dizziness and vertigo. The second component with 20% of the variance had high loadings of utricular asymmetry with hearing loss, negatively associated with age indicating utricular dysfunction occurring in the older patient who suffered more deafness. Component 3 (15.5% variance) associated canal paresis with hearing loss, particularly occurring particularly in males and 4 (14.3% variance) associated duration of disease with high levels of tinnitus. This

Component	Initial Eigenvalues		
	Total	% of Variance	Cumulative %
1	2.281	25.341	25.341
2	1.818	20.203	45.544
3	1.399	15.548	61.092
4	1.287	14.3	75.391

Table 5.3 showing significant results of Factor analysis

pattern of associations is descriptive of the typical presentation of the disease with the addition of utricular and canal functional statuses. This is a very small sample for detailed analysis and these findings should be treated as provisional findings.

One would think that vertiginous episodes indicates labyrinthine activity and hence would expect to find either diminished hearing or worse levels on vestibular testing like caloric or utricular function testing but this was not the case. The following graphs show the varying relationship between hearing loss, vestibular function and number of attacks, where the number of attacks are depicted in decreasing order.

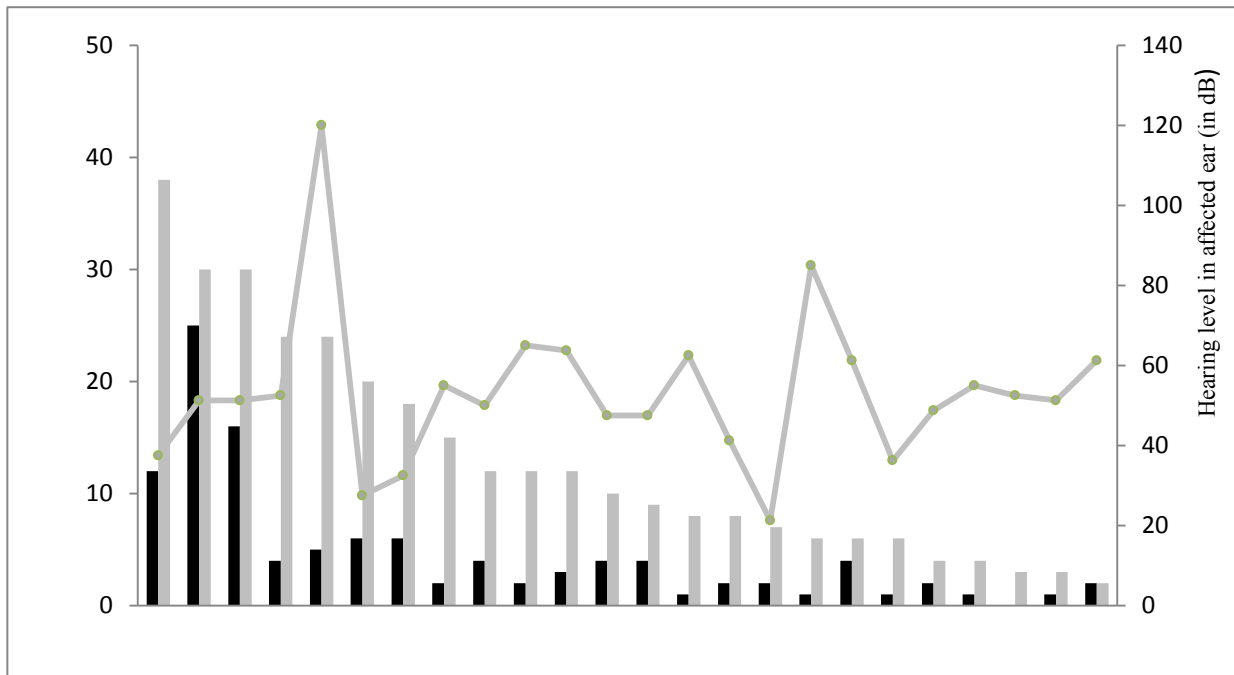


Fig 5.1 showing relation between number of vertigo attacks in individual patient (in last six months- gray vertical bars; in last one month- black vertical bars) and average pure tone hearing levels in the affected ear in dB. Hearing loss was independent of the actual number of vertigo attacks. (n=24).

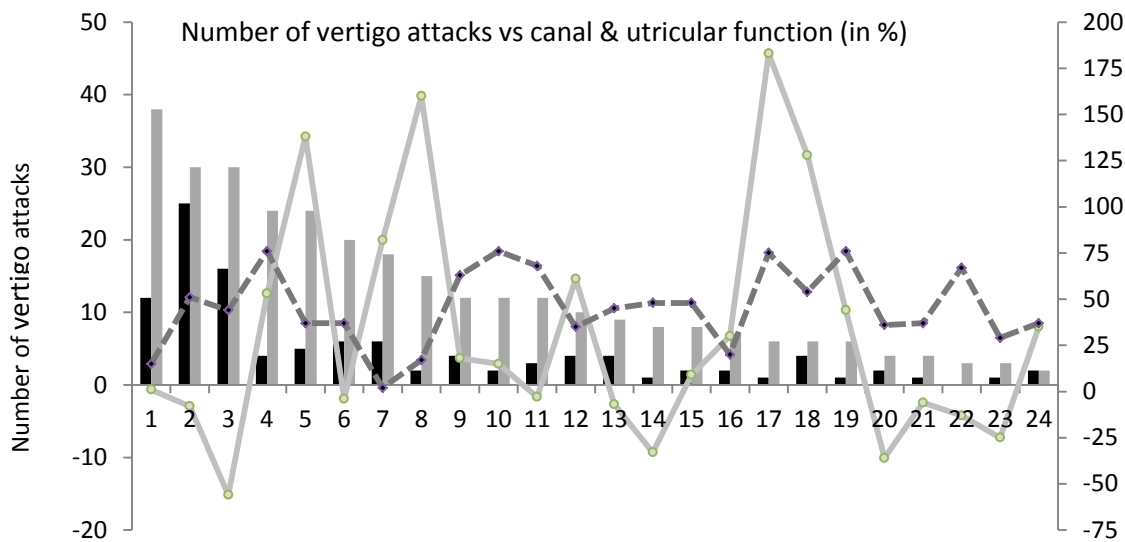


Fig 5.2 showing no relation between self- reported number of vertigo attacks in individual patient (in last six months –gray vertical bars; in last one month- black bars) and caloric paresis (black line) and utricular asymmetry (gray line) in terms of % of functional canal and utricular loss. (n=24).

5.4 Discussion:

In the light of the new knowledge of utricular function abnormalities, we wanted to investigate if there was a significant relationship between self-reported symptoms and observed utricular function. However, none was found.

The questionnaire data suggest moderate to severe impairment of daily life due to audiovestibular symptoms. The scores were higher for vertigo and dizziness questionnaires compared to tinnitus and aural fullness which is similar to Cohen et al, 1995 reporting vertigo being the most disturbing symptom of Ménière’s disease followed by hearing loss. Also, uncertainty of the vertigo attacks is the key factor for higher levels of anxiety, depression and feeling of handicapness (Kirby and Yardley, 2012) and our questionnaire assessments do

reflect the same relationships. Additionally, vertigo is also known to be most intrusive of tinnitus or hearing problems by self-reported measures in 74 participants of Ménière's Society in UK contacted through their magazine (Arroll et al, 2012). They reported that the symptoms of Ménière's disease, chiefly vertigo is highly intrusive ranking only fifth among 37 highly intrusive illnesses. 'A propos', the more intrusive illnesses than vertigo were fibromyalgia, HIV, anxiety, chronic fatigue syndrome. There is also significant correlation between different questionnaires and overlap of symptoms which is understandable. This might imply difficulty in differentiating one symptom from other and the add on effect on overall disability and emotional wellbeing. This implies that management has to be targeted in understanding these psychological domains when addressing management of the chronic inner ear disease.

The hydropic changes are now universally accepted to be the pathophysiological phenomenon to explain the characteristic features of Ménière's disease. Also, the differential loss of audiovestibular function in the affected ear is supported by histopathological and radiological studies. There is a common assumption that the audiovestibular function will be poor in the affected ear when the disease is active, i.e. when the function is measured around the period of Ménière's attacks. But although we studied patients in an active phase of the disease, we still did not find evidence for concurrent impairment of auditory and vestibular function. With a mean number of 5 (sd6) vertigo attacks in the last month suggests that patients were indeed in active phases. It is more than surprising to find a clear mismatch between what patients are describing which form the crux of the diagnosis and what clinicians and audiovestibular physiologists are reporting to confirm the diagnosis.

The unexpected finding of overall poor correlation between reported symptoms, disease activity and audiovestibular function can have numerous explanations. However, there are few other studies who had reported similar findings, for example, McNeill et al did not find

any significant change of hearing level on pure tone audiometry in five out of six affected ears 24 hours before, during, after 24 hours of a Ménière's attack. One subject in their group had some change in hearing few minutes before the attack which improved 12 hours after the attack. On the other hand, Proctor, 2000 found that shortly after an acute attack of vertigo, only one of eight Ménière's disease patients showed a decreased caloric response whereas four of them showed an increased response on the diseased side. It is therefore hypothesized that the pathophysiological mechanisms producing symptoms and producing end organ damage are different. Also, Murray et al, 2007 failed to find any difference between groups in dizziness handicap inventory with horizontal canal disorder with or without otolith dysfunction. They had defined otolith dysfunction on basis of abnormal VEMPs or abnormal static bias (subjective visual vertical or horizontal) along with horizontal canal dysfunction on caloric testing. It also reported that there is a significant difference between perceptual tasks and peripheral audiovestibular function, a phenomenon becoming more and more observed in audiovestibular medicine (Seemungal, 2014). The surprising correlation between aural fullness and better speech scores is confusing as more aural fullness should show drop in scores. Does this show mismatch of the perception vs peripheral response? Alternatively in Ménière's disease it might also indicate that less fullness may indicate 'burnt out' ear and hence poorer speech discrimination. As there was no relation between duration and speech scores or aural fullness, how long an ear takes to 'burn out' could be independent of duration but vary according to original damage mechanism and its speed of progression.

A significant relation between poor hearing and worse dizziness handicap inventory scores was also found. The hearing loss was measured as average hearing level in low frequencies (0.5,1,2 and 3kHz) using pure tone audiometry. Dizziness handicap inventory is the most widely used self-reported measurement of dizziness in patient population. And we have already noted a significant relationship between hearing function and canal paresis, between

hearing and utricular function in the previous chapter. Stepwise regression analysis also showed hearing loss to be a predictor of poorer utricular function ($F_{6.1}$, $df\ 2/22$, $p < 0.1$, adjusted $R\ 0.3$). It might indicate cochlear function even though not directly contributing to dizziness but more sensitive end organ measure probably indicating that hydrops commonly begins in cochleo-saccular part of labyrinth and vestibular symptoms may be apparent before vestibular damage can be detected by vestibulometric tests.

A further consideration is that fluctuation is a key characteristic of Ménière's disease and although we did not find correlation between disease activity, symptoms and function- all of them were independently significantly impaired. Ménière's is a chronic disease and it probably affects function over a long period of time rather than just around attacks. This might indicate functional resilience of the inner ear which is affected over a long period of time rather than just during short bursts of disease activity. The natural history of the disease of decline in audiovestibular function is long known now. So, if the function is well preserved but symptoms are significant, it clearly suggests that further management and rehabilitation should be actively pursued, not only to manage symptoms but also to promote overall balance function in the long term.

Chapter 6

Visual Dependence and BPPV

6.1 Introduction

In specialised neurology, ENT and neuro-otology clinics it is common to see patients with long standing symptoms of dizziness, the onset of which can be traced to acute symptoms of vertigo months to years previously (Bronstein, et al, 2010; Brandt et al, 2010). Although there is no consensus on a diagnosis for these patients, explanations for the prolongation of symptoms range from psychological disorders (Faralli et al, 2009; Ferreira et al, 2010) to defective central compensation of the initial peripheral vestibular insult (Shupak et al, 2008; Palla et al, 2008). Amongst reasons for the latter, several authors have hypothesised that increased reliance on, or high sensitivity to, visual input could interfere with full vestibular recovery in some patients. These patients are thought to be ‘visually dependent’ and the syndrome has received different names, such as space and motion discomfort (Jacob, 2009), visual vertigo (Bronstein, 2004), visuo-vestibular mismatch (Longridge and Mallinson 2005), visually-induced dizziness (Bisdorff, 2009).

The concept of visual dependence stems from the original work of Witkin and Asch (Witkin and Asch, 1948; Guerraz et al, 2001, see review in Witkin 1959) who observed that, in situations of conflict between sensory modalities involved in spatial orientation, some subjects choose to rely predominantly on visual input. These otherwise normal individuals, called field- or visual-dependent, are more likely to be disoriented or destabilised by tilted or moving visual surroundings. At a clinical level, it has been noted that vestibular patients whose dizzy symptoms are triggered or aggravated by such visual scenarios (hereinafter Visual Vertigo or VV) also show increased visual dependence when measured with

techniques which are commonly used (Guerraz et al, 2001). The current study examines how visual dependency develops following vestibular symptoms, using the BPPV attack as a model. This is relevant with rest of the work in this study as utricular function was measured studying tilt perception using subjective visual vertical. SVV reading can be affected by visual dependency and can be a potential confounding factor.

The combination of a vestibular disorder with increased visual dependence seems to underlie the appearance of VV symptoms. Two pathways can be postulated that would lead to this syndrome; either these patients were visually dependent before the vestibular insult, or the vestibular episode triggers an enhancement in visual dependence. In order to examine the latter hypothesis in the laboratory, we measured visual dependence in patients with BPPV before and after the positional manoeuvres. The underlying question is whether visual dependence is a neural, highly plastic trait or susceptibility that can be modified by brief vestibular excitation or dysfunction.

6.2 Materials and methods

Experimental strategy:

In order to address the research question we measured visual dependence, before and after a Hallpike manoeuvre (and repositioning procedures if appropriate) in patients with active BPPV ('Positive Hallpike manoeuvre' or 'PosH' group) and in two control groups: an age matched normal control group and a patient control group which included patients with a clinical history fully compatible with BPPV but in whom the Hallpike manoeuvre did not induce vertigo or nystagmus (the 'Negative Hallpike manoeuvre' or 'NegH' group).

Patients with a clinical history suggestive of active BPPV (i.e. brief vertigo episodes triggered by head movements such as looking up/down, bending forwards, lying down or turning over in bed) were recruited into the study. The working diagnosis was BPPV in all patients and it remained so after a standard clinical neuro-otological examination (not including the Hallpike manoeuvre positional manoeuvre which was purposefully delayed, see next). The experiments for the study were carried out in a single test session. After the subjects had performed all of the experimental perceptual and postural tasks, Hallpike manoeuvre manoeuvres were carried out. If the Hallpike manoeuvre response was positive, the appropriate treatment repositioning manoeuvres were performed. All subjects then repeated the experimental tasks.

Note that patients who were diagnosed with active BPPV ('Positive Hallpike manoeuvre' or 'PosH' group) underwent both the Hallpike manoeuvre and repositioning manoeuvres before repeating the experimental tasks. The treatment was done before repeating experimental tasks as we would normally proceed with the treatment following the diagnosis in the clinics. The subjects were free to withdraw from the study at any stage. However, to avoid confusion the results have been uniformly labelled as post Hallpike manoeuvre for all the three groups.

Twenty patients with a positive Hallpike manoeuvre response were assigned to a 'PosH' group; typical positional nystagmus was directly observed in all cases by experienced neuro-otologists. The affected semicircular canals were: right posterior in 9 patients, bilateral posterior in 6 patients, left posterior in 2 patients, right anterior in 2 patients, and left anterior in 1 patient. CNS disease in the anterior canal BPPV patients was ruled out by neurological examination and MRI.

Dix-Hallpike manoeuvre manoeuvre is a well recognised test (Dix and Hallpike, 1952; Kaski and Bronstein, 2014) for provoking and confirming the diagnosis of BPPV. The patient is sat

upright on an examination couch with head turned 45 degrees towards the examiner. The next step is to move the patient swiftly to a lateral head hanging position. In positive cases, nystagmus is observed after a brief latency of few seconds, the intensity increases and then decreases within 30seconds. The patient usually confirms that the dizziness experienced resembles their own. The direction of the observed nystagmus helps to ascertain the semicircular canal which is affected by the floating debris. In the typical posterior canal BPPV the nystagmus is predominantly torsional, with eyes beating towards the undermost ear interspersed with upbeats (Kaski and Bronstein, 2014). Anterior canal BPPV is much less common and the nystagmus is predominantly vertical downbeating with other characteristics of a BPPV nystagmus (latency, crescendo-decrescendo, symptomatic). MRI scan is organised in any case of downbeating nystagmus (Bertholon et al, 2002).

In the 20 patients in the 'NegH' group, the Hallpike manoeuvre manoeuvres did not provoke any nystagmus. Twenty subjects with no history of vestibular or neurological disease, were also tested before and after Hallpike manoeuvre manoeuvres (normal control group).

The mean $\pm$ standard deviation of the ages for the subject groups were: PosH 60.0 ± 13.7 years, NegH 52.8 ± 13.7 years, Normal Controls 54.8 ± 11.6 years. Duration of symptoms ranged from 3 months to 25 years. The PosH and Normal Control groups each comprised 16 females and 4 males; the NegH group comprised 14 females and 6 males. All subjects provided informed consent to participate in the study, which was approved by the Imperial College Healthcare ethical committee.

Experimental Apparatus and Techniques:

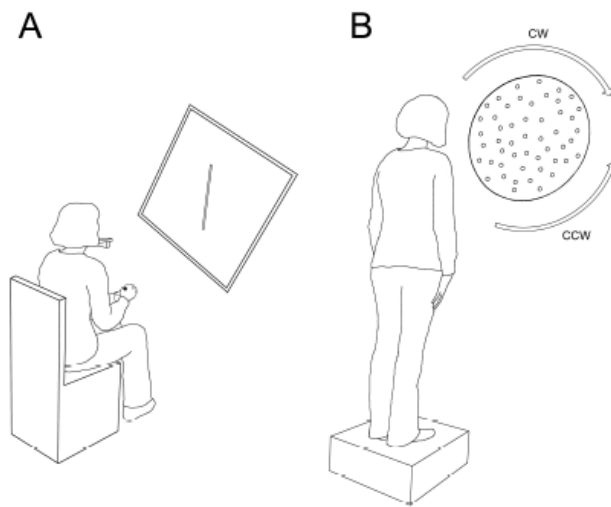


Fig 6.1 showing experimental setup. (A) Rod and Frame test with tilted frame. (B) Postural sway recording during viewing a disc decorated with luminous spots for visual roll-motion stimulation. The safety harness has been removed for illustration purposes. Arrows indicate the motion directions for the two disc rotation conditions, clockwise (CW) and counter-clockwise (CCW).

Rod and Frame

The Rod and Frame test measures static visual dependence (Witkin and Asch, 1948). Subjects were seated in a dark room, in front of a fluorescent rod (40 x 0.5cm) which rotated about a motorised bearing through the rod centre. The rod was mounted centrally within a fluorescent square frame (90 x 90cm, edge width 2.4cm). The subjects used a chin rest, and the centre of the rod was aligned with the subject's eye level, at a distance of 80cm. The subjects were able to control the orientation of the central rod remotely with a rotating knob. At the beginning of the test, the frame was masked and the subjects had to align the rod with gravitational vertical – the subjective visual vertical (SVV) task. The starting position of the rod was about 40°,

either to the left or the right, and there were 6 trials. The subjects then repeated the SVV task with the fluorescent frame visible (Figure 1A). The frame was tilted by 28° , to the right or the left in a counterbalanced order across subjects, and subjects were instructed to ignore the frame and set the central rod to gravitational vertical as before. ‘Frame Dependence’ was defined as the average tilt of the SVV in the direction of frame tilt.

Rod and Disc

The Rod and Disc test measures dynamic visual dependence. Subjects were seated in a dark room, in front of a fluorescent rod (20 x 0.5cm) surrounded by a disc (90cm diameter) covered with a random array of fluorescent dots. The subjects used a chin rest and the centre of the rod was aligned with the subject’s eye level, at a distance of 80cm. Rod orientation was controlled remotely with a rotating knob. Initially, subjects performed a simple SVV task and then repeated the SVV task with the background disc rotating at $30^\circ/\text{s}$, clockwise and counter-clockwise in a counter-balanced order. ‘Disc Dependence’ was defined as the average tilt of the SVV in the direction of disc rotation.

Postural Sway

Subjects stood bare-foot on a force platform, secured by a harness. Their feet were placed on footprints drawn at an angle of 30° , with heels 7cm apart. The disc was positioned at eye level in front of the subjects, at a distance of 80cm, and the SVV rod was masked using a black disc with a central fluorescent spot (Figure 1B). Postural sway was recorded as displacement of the centre of foot pressure in the lateral and anteroposterior directions. Three different visual conditions were used: 1) Eyes Open (EO) – subjects fixated the central target in full room illumination for 45s; 2) Eyes Closed (EC) – 45s recording; 3) Disc Rotation (Rotn) – the room was darkened, so that the subjects were only able to see the fluorescent spotty disc and central fixation target (Figure 1B). The disc was stationary for 15s, then

rotated for 45s at a velocity of 30°/s clockwise and counter-clockwise. During the different visual conditions, subjects were instructed to stand still and be relaxed with their hands at their sides. EO sway was recorded initially, followed by EC sway, and then the two directions of disc rotation were presented in a counter-balanced order. The total sway paths (defined as the X-Y summed motion path of the centre of foot pressure) in each trial were calculated; the sway paths of the two Disc Rotation conditions were averaged, to represent the Disc Rotation-induced sway. The Kinetic Quotient was defined as the ratio of sway paths in the Disc Rotation and EO conditions ($KQ = Rotn / EO$); this quantifies the destabilizing effect of a moving visual stimulus.

Questionnaires

All subjects completed the Dizziness Handicap Inventory (DHI), Vertigo Symptom Scale (VSS), Situational Vertigo Questionnaire (SVQ), Motion Sickness Susceptibility Questionnaire Short Form (MSSQ-Short) and a general health questionnaire. Questionnaires were completed only once, before the experiments.

The Dizziness Handicap Inventory (Jacobson and Newman, 1990) measures how vertigo and imbalance affect an individual's quality of life. The Vertigo Symptom Scale (Yardley et al, 1992) was used to rate the type and frequency of symptoms over the previous month. It yields two scores: (i) for vertigo and imbalance (e.g. 'feeling that things are spinning or moving around'), (ii) for autonomic and somatic anxiety symptoms (e.g. 'heart pounding or fluttering', 'excessive sweating'). The Situational Vertigo Questionnaire (Guerraz et al, 2001) rates how strongly a subject's symptoms are affected by disorientating environments, especially those with visual-vestibular conflict. The Motion Sickness Susceptibility Questionnaire (Short Form) (Golding, 2006) predicts individual differences in motion sickness by rating the frequency of nausea induced by various types of transport and

playground rides, in childhood and over the last 10 years. The general health questionnaire is an in-house medical screening questionnaire, including headache frequency and characteristics based on the International Headache Society classification (Headache classification subcommittee, 2004).

Statistical analysis:

All statistical analyses were performed using the SPSS software package. Linear regression was used to check for age-dependent effects in the data (Pearson's correlation coefficient). General Linear Model (GLM) repeated measures analysis was used to compare subject groups, as all variables had been measured pre- and post- Hallpike manoeuvre manoeuvres. Age was included as a covariate where a significant correlation had been found. When GLM showed significant values, ANOVA was used to investigate group differences in particular conditions, e.g. postural sway, Eyes Closed, post Hallpike manoeuvre manoeuvre. The Kruskal-Wallis and Mann-Whitney tests were also used to investigate group differences in the postural sway task with the rotating disc; these non parametric tests were used because many patients were not able to complete this particular task hence creating large inequalities in subject numbers amongst the three groups (see Results). Paired t-tests and non-parametric Wilcoxon signed rank tests were used to look for within-subjects pre-post changes, according to whether the preceding test was parametric (GLM/ANOVA) or non parametric (Kruskal-Wallis). When comparing frequency of clinical abnormalities in different subject groups the Fisher's exact test was used.

6.3 Results

We first present the experimental data in the three groups (normal control, PosH and NegH), which was the original aim of this project. And then a summary of clinical findings of the

NegH group with aiming to reach a diagnosis in these patients with a history of BPPV but normal Hallpike manoeuvre manoeuvre.

Experimental results:

Postural sway during quiet stance (EO and EC conditions):

Not all subjects were able to complete the postural sway tasks. In each patient group, 17 subjects completed the EO condition and 16 subjects completed the EC condition. All normal subjects were able to complete the EO and EC trials, but sway data from 1 normal subject was lost due to technical reasons.

During quiet stance, for all subjects combined, there was an increase in sway with age ($r>0.40$, $p<0.005$). GLM repeated measures analysis, with age as a covariate, showed that there was a sway difference between the subject groups in the EC condition ($F=3.69$, $p=0.03$), and ANOVA confirmed that PosH patients swayed more than normal controls after the Hallpike manoeuvre manoeuvre ($p=0.01$).

Static visual dependence (Rod & Frame test):

Most subjects tilted the SVV in the direction of the tilted frame. Frame dependence increased with age for both patient groups ($r>0.46$, $p<0.04$), but there was no significant correlation for the normal controls.

There was no significant difference in frame dependence between the subject groups. Overall, frame dependence decreased post-Hallpike manoeuvre ($F=8.70$, $p=0.005$). However, on paired t-tests, only the normal control group showed a significantly reduced frame dependency post-Hallpike manoeuvre manoeuvring ($t=2.39$, $p=0.03$).

Dynamic visual dependence:

Rod-and-Disc test

Only 18 subjects in each of the patient groups were able to complete the Rod and Disc test, the other subjects became too disoriented by the rotating disc; all of the normal subjects completed the task. Most subjects tended to tilt the SVV in the direction of disc rotation. Disc dependence increased with age for all subject groups ($r>0.45$, $p<0.05$).

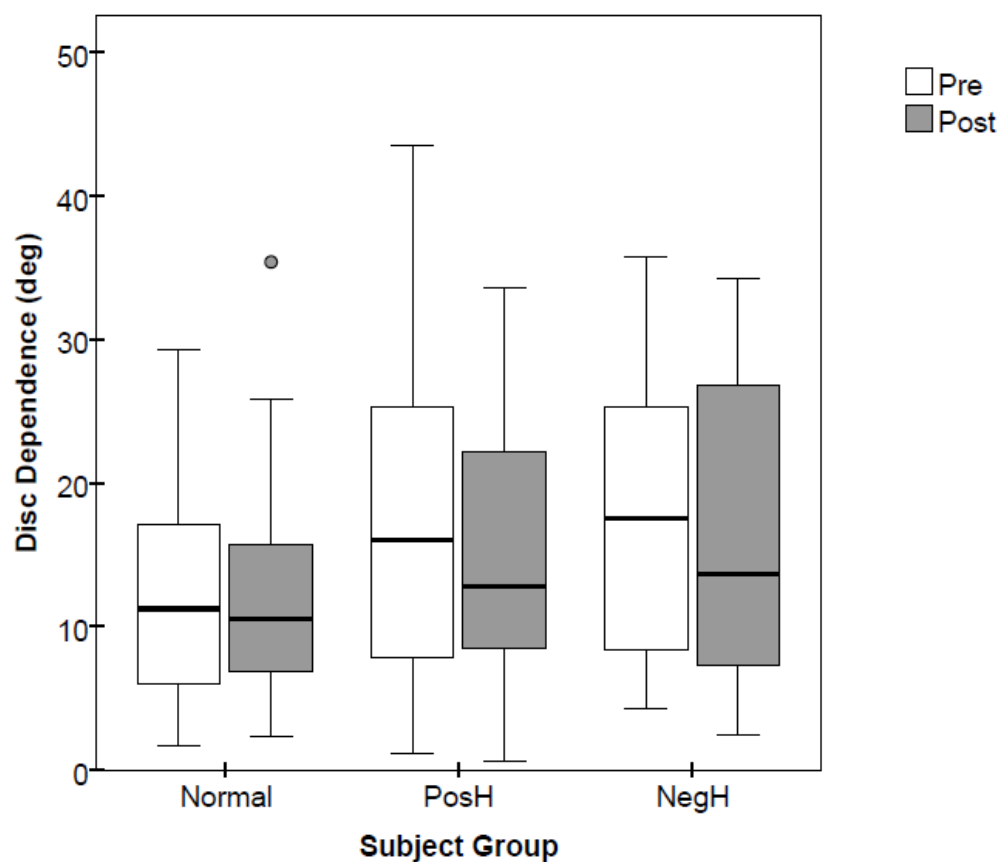


Figure 6.2

Disc dependence: The vertical line represents degrees of tilt of the SVV during background disc rotation. The line inside each box represents median values; the length of the box, interquartile ranges; circle/s represents outliers. Only the PosH group showed a significantly reduced disc dependency post-Hallpike manoeuvre.

Repeated measures analysis, with age as a covariate, showed that there was a difference in disc dependence between the subject groups, which is increased in patients as shown in Figure 2 ($F=3.52$, $p=0.04$). There was no significant change in disc dependence post-Hallpike manoeuvre overall but, on paired T-tests, the PosH patients showed a significantly reduced disc dependency post-Hallpike manoeuvre (mean reduction $2.8^\circ \pm \text{sd } 5.6^\circ$, $t=2.13$, $p=0.05$).

Disc-Postural test

Some subjects were unable to complete the postural sway task in front of the rotating disc, due to severe dizziness. 16 PosH patients completed the trials, but only 13 NegH subjects were able to tolerate the stimuli. One normal subject was unable to perform the task, and sway data from another normal subject was lost due to technical reasons.

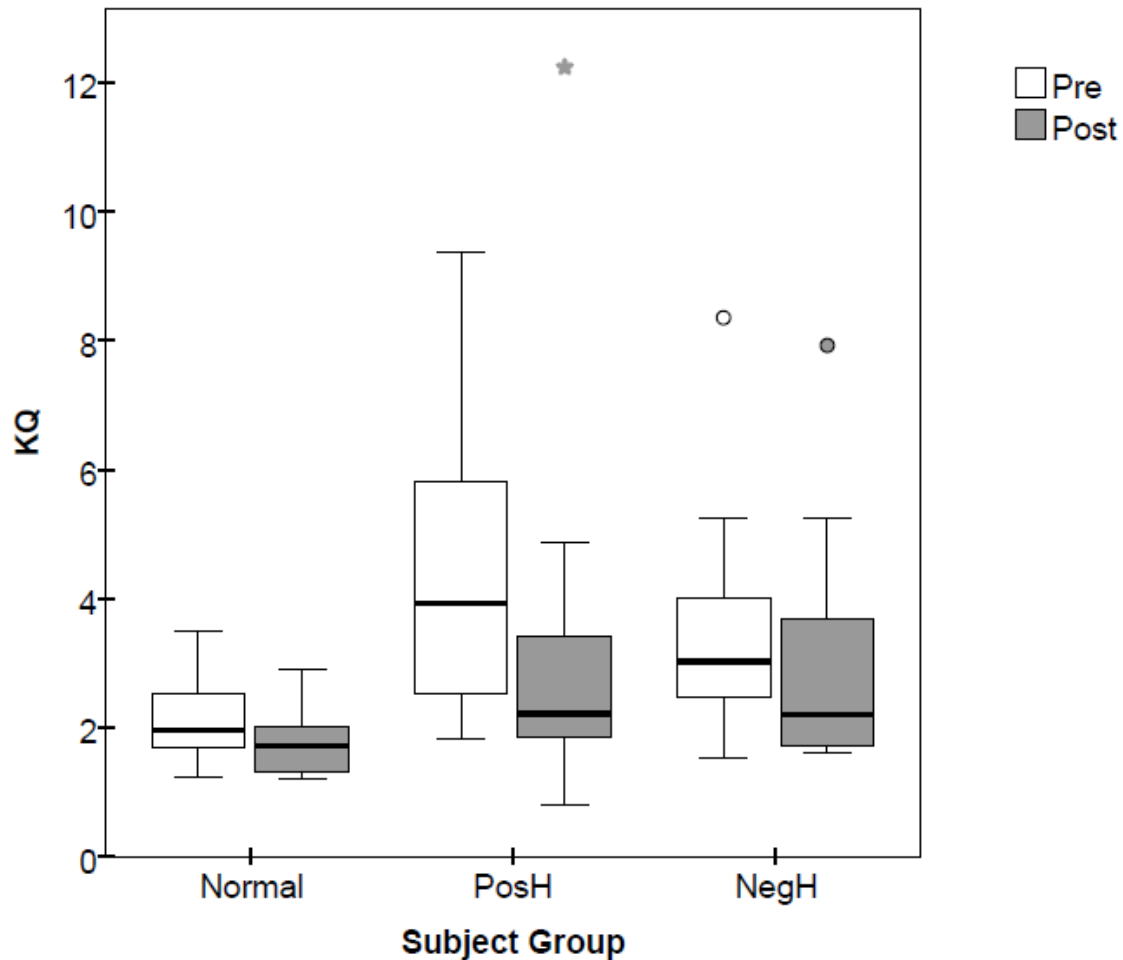


Figure 6.3

Kinetic Quotient (KQ). Symbols as in Fig 2, plus the asterisk represents an extreme outlier. Both patient groups had a higher KQ than normal controls. KQ decreased post-Hallpike manoeuvre for the normal controls and the PosH group, but there was no significant change for the NegH group.

Subjects swayed more when the disc was rotating than when it was stationary, i.e. the Kinetic Quotient (KQ), defined as the ratio of sway paths in the disc rotation and disc stationary conditions ($KQ = \text{Rotn} / \text{EO}$), was greater than 1. Repeated measures analysis showed that both patient groups had a higher KQ than normal controls ($p < 0.05$), i.e. patients were more

destabilized by the rotating disc than the normal controls (Figure 3). However, group differences were mostly investigated using non-parametric statistics, because of the high number of patients unable to complete the postural sway tasks with the rotating disc (unequal sample size). The Kruskal-Wallis test showed group differences in KQ, both pre-Hallpike manoeuvre (chi-square= 14.15, $p=0.001$) and post-Hallpike manoeuvre (chi-square=8.99, $p=0.011$). Mann-Whitney tests highlighted significant differences in KQ between the PosH and normal control groups (pre-Hallpike manoeuvre $U=43$, $p<0.001$; post-Hallpike manoeuvre $U=69$, $p=0.01$), and also between the NegH and normal control groups (pre-Hallpike manoeuvre $U=50$, $p=0.007$; post-Hallpike manoeuvre $U=55$, $p=0.013$). There were no significant differences in KQ between the two patient groups.

Overall, sway path and KQ decreased post-Hallpike manoeuvre (sway path $F=8.98$ $p=0.004$; KQ $F=8.67$ $p=0.005$), probably a habituation effect. The non-parametric Wilcoxon signed rank test showed a significant reduction in KQ for both the normal controls ($Z=-2.59$, $p=0.01$) and the PosH group ($Z=-2.33$, $p=0.02$), but not for the NegH patients.

Questionnaires:

There was no significant difference between subject groups on the motion sickness susceptibility scales. As expected, however, the patient groups had significantly higher scores than the normal controls on the Dizziness Handicap Inventory, Vertigo Symptom Scale and Situational Vertigo Questionnaire (DHI $F>56$ $p<0.001$; VSS $F>29$ $p<0.001$; SVQ (normal vs PosH) $F=4.72$ $p=0.036$; SVQ (normal vs NegH) $F=14.11$ $p=0.001$). There were no significant differences between the patient groups.

Scores on the Dizziness Handicap Inventory, Vertigo Symptom Scale and Situational Vertigo Questionnaire were all correlated with dynamic visual dependence and KQ (all statistics $r>0.36$, $p<0.012$).

Clinical summary of the NegH group:

Incidence of migraine and final diagnosis of the patient control group:

In this group, 10/20 patients had positional symptoms so typical of BPPV that this remained as first diagnosis despite the negative positional test. In 5 other patients, additional differential diagnoses were considered: migrainous vertigo ($n=2$), orthostatic hypotension ($n=1$), bilateral vestibular failure ($n=1$; confirmed on rotational responses), past vestibular neuritis ($n=1$). For the remaining 5 patients, BPPV also stayed as the most likely diagnosis, modified in its expression by additional features (anxiety $n = 2$; past migraines $n = 3$). MRIs were carried out in 10 patients but these were either normal ($n= 6$) or showed non relevant incidental findings ($n= 4$; mild small vessel white matter disease in two patients, a mature parietal-thalamic infarct and an empty sella).

Seventeen patients from the NegH group underwent one or more vestibular function tests (bithermal calorics or rotational testing) which showed that only 3/16 (19%) patients had abnormal vestibular function (a patient did not tolerate any laboratory vestibular test). Since a diagnosis of BPPV is essentially clinical, vestibular function was assessed in only 9 patients from the PosH group, which showed that 6/9 (67%) patients had abnormal results. The incidence of vestibular function abnormalities was thus significantly lower in the NegH than in the PosH group (Fisher's exact test, $p = 0.03$).

Table 6.1 : Clinical findings in the PosH and NegH patient groups. Tests

	PosH group	NegH group	Significance values (Fisher's exact test)
Abnormal vestibular function*	6/9 (67%)	3/16 (19%)	p= 0.031
Migraine on questionnaire assessment	3/20 (15%)	9/20 (45%)	p= 0.082

*Vestibular function assessed by caloric testing or rotational ENG (if caloric not tolerated or contraindicated). The caloric test is considered abnormal if weakness is more than 25%.

The general health screening questionnaire allowed an assessment of whether subjects had migraines or not (according to the International Headache Society 2004 criteria). The results for the patient groups are displayed in Table 1. In the normal controls, only one subject had migraine. The proportion of migraineurs in the NegH group (45%) was higher than the reported prevalence of migraine in a general population (mean prevalence = 14.7%; Stovner and Andree 2010) and higher than in the PosH group (15%; short of two-tailed statistical significance, Fisher's exact test p=0.082).

The NegH group patients were followed up as they did not have a definitive diagnosis. Sixteen patients were phone interviewed within 5 years, but 4 patients were lost to follow-up; 12/16 of the patients still reported positional-like symptoms and 9 of these were reassessed in clinic. The Hallpike manoeuvre was negative in 6/9 patients for both symptoms and signs. One patient was symptomatic (without nystagmus) on the right side positional manoeuvre and was treated with the Semont manoeuvre on two separate days, unsuccessfully. Another patient showed a few beats of downbeat nystagmus on positional testing; MRI scan was normal. Finally one patient developed panic during the Hallpike

manoeuvre without nystagmus and did not tolerate further vestibular testing. No patient had a positive Hallpike manoeuvre with typical nystagmus for BPPV.

6.4 Discussion

This study was designed to see whether visual dependence can be modified by a brief exposure to vertigo. The vertical canals BPPV model was deemed relevant because standard measures of visual dependence rely on tilting or rotating visual objects in the frontal (roll) plane. So, both the vestibular and the visual stimuli act in similar (though not identical) spatial coordinates. The first part of the discussion will consider whether visual dependence is a plastic (adaptive) phenomenon such that it can be modulated by a single attack of BPPV. In the second part we will discuss an issue that was not part of our original research question - what are the differences between patients with positional vertigo in the positive (PosH) and negative Hallpike manoeuvre (NegH) groups?

Can visual dependence be modulated by a brief positional vertigo attack?

Some patients with long term vestibular symptoms and visual vertigo (visually-induced dizziness; (Bisdorff et al, 2009)) have increased visual dependence, as assessed with the techniques used here. This cannot be explained by the presence or degree of the vestibular deficit, since patients with visual vertigo become more destabilized by moving visual stimuli (higher kinetic quotient) than patients with absent vestibular function (Guerraz et al, 2001).

The symptoms of visual vertigo may result when a person with a pre-existing high visual dependence trait is struck by a vestibular disorder. Vestibular neuritis, migraine or BPPV are extremely common and visual dependence is a normally (Gaussian) distributed variable in the normal population. Viewed statistically, a proportion of vestibular patients would be prone to

develop visual vertigo by the simple chance occurrence of two common phenomena. The psychological aspects also play important role in the development of chronic dizziness (Furman and Jacob, 2001; Staab and Ruckenstein, 2009; Best et al, 2009).

Alternatively, the high visual dependence may develop as a consequence of the vestibular insult. A degraded vestibular input would lead to enhanced reliance on visual input, a process that in some patients might be upregulated. For this reason we measured visual dependence in patients before and after a BPPV attack to see whether the brief but intense vertigo in BPPV was capable of inducing changes in the variables measured. If some patients developed unusually high levels of visual dependence in response to the BPPV vertigo, this would be strong support for this alternative hypothesis.

We found that both groups of patients, PosH and NegH groups, had enhanced postural responses to the rotating disc. This confirms that, when vestibular signals are unreliable visual dependence increases by a process of sensory reweighting (Guerraz et al, 2001, Fetsch et al, 2009). What we did not find, however, is a further increase in visual dependence in the PosH patients when they were retested after the positionally-induced vertigo. Hence, a single attack of BPPV does not increase visual dependence.

Quite the contrary, the trend in the whole population studied was for a decrease in the visually-induced effects following the Hallpike manoeuvre manoeuvre. This is not due to the positional and re-positioning manoeuvres per se since one of the strongest reductions in the visually-induced effects was observed in the normal control subjects in whom the positional manoeuvre has no sensory-motor consequences. The most likely explanation is an adaptation to the repetition of the visual motion stimuli, in agreement with previous work in normal subjects (Bronstein AM, 1986; Pavlou M, 2011). It has to be borne in mind that the effects

induced by visual stimuli of the kind used in this study (i.e. large field, moving, disorienting stimuli) are linked to the fact that they can generate sensations of self-motion (Mast F, 2001; Guerraz and Bronstein, 2008). As the expectation of self-motion decreases on repetition of the same visual stimulus, postural responses diminish in amplitude. The significance of the current findings is that we now report, for the first time, reductions in visual dependence not only in normal (Pavlou et al, 2011) but also vestibular subjects. The finding has implications for the visual motion therapy of vestibular patients as it can be postulated that the improvement induced by such therapy (Vitte, 1994; Pavlou et al, 2004) may be mediated by a reduction in visual dependency.

Finally, visual dependence data obtained during the perceptual tasks showed an age effect - the influence of the tilted frame and the rotating disc on the subjective visual vertical increased as a function of age. This was observed for all subject groups in the Rod and Disc test, and for both patient groups in the Rod and Frame test. An increase in visual dependence in the elderly can be explained by their increase in proprioceptive (Bergin et al, 1995) and vestibular (Seemungal et al, 2004) thresholds. Indeed, intact vestibular (Bronstein et al, 1996) and proprioceptive systems (Bronstein, 1986) exert a restraining effect on visual motion-induced effects (Black and Nashner 1984; Peterka and Benolken, 1995). The finding that the correlation with age was present for seated tasks (Rod and Frame; Rod and Disc) but not during standing upright tasks (Kinetic and Romberg Quotients) is intriguing and it may suggest that a primary increase in visual dependency (i.e. not secondary to vestibular-somatosensory loss) develops as we age.

Differences between the NegH and PosH groups

The patient control group (NegH) responded differently to the BPPV patients (PosH group) during our experiments. Despite the fact that 13/16 patients in the NegH group had normal vestibular function tests (Table 1), they showed increased visual dependence both perceptually (Figure 2) and posturally (Figure 3). Further, they were the only group not reducing the magnitude of the visuo-postural responses on re-testing (Figure 3). The conclusion is that the NegH group, despite having less vestibular impairment than the PosH group, showed enhanced visual dependence. In agreement, they scored highly on the Situational Vertigo Questionnaire indicating a higher degree of ‘visual vertigo’ symptoms.

The NegH patients, initially recruited just as a control group to ‘true’ positive Hallpike manoeuvre BPPV, constitute a difficult but interesting diagnostic group - what is the underlying diagnosis in these patients? The first possibility is that they indeed have true BPPV, albeit with a normal Hallpike manoeuvre on the day. This so-called ‘subjective BPPV’ is not uncommon (Balatsouras and Korres, 2011) and potential causes for the normal Hallpike manoeuvre are self-habitation during spontaneous head movements, small amounts of otoconia (Haynes et al, 2002) or its atypical location within the affected canal (Buki et al, 2011). However, there are reasons to believe this was not the case for many of our patients. Most patients (12/16) continued with positional vestibular symptoms but in the nine re-examined none showed BPPV. Notably, the frequency of migraine was higher in this group. Other studies have reported links between vestibular migraine and positional nystagmus (Polensek and Tusa, 2010), confirmed to be due to vestibular migraine during acute attack observations (von Brevern et al, 2004). It is possible that at least some patients in the NegH group suffered from a positional form of vestibular migraine (9/20; Table 1). The fact that vestibular testing was usually normal (13/16 patients) is also compatible with this diagnosis. It could be argued that a limitation of this (unplanned)

part of our study is that formal diagnostic criteria for vestibular migraine (Neuhauser and Lempert, 2005 and 2009) were not applied but this diagnosis was an afterthought. Indeed, if patients had fulfilled formal criteria for vestibular migraine they would not have been included as a control group for BPPV patients for our study. The findings do suggest however that some patients with positional vertigo but normal Hallpike manoeuvre manoeuvre may suffer from a specific form of migraine but this will need to be explored prospectively.

6.5 Conclusions

In summary, this study shows that a single BPPV attack does not increase visual dependence. Baseline levels of visual dependence are higher than normal in patients with positional vertigo symptoms, whether the Hallpike manoeuvre diagnostic test is positive or negative. Whether this represents a form of otolith compensation or not, only future research will be able to answer. The question of whether the exaggerated visual dependence seen in visual vertigo patients is a pre-morbid trait or triggered by the vestibular disorder remains unanswered. Visual dependency reflects neural plasticity because a labyrinthine disorder as it was enhanced in the presence of BPPV and reduced by repeated visual stimulation. The latter also suggests that the clinically useful effects of visual desensitization therapy previously reported may be mediated by progressive decrements in visual dependence levels. Finally, an interesting group of patients with symptoms of positional vertigo, negative Hallpike manoeuvre manoeuvre and increased levels of visual vertigo and visual dependence was identified. The increased incidence of migraine amongst them, the frequent normality of the vestibular tests and the lack of an alternative diagnosis, suggests that the positional vertigo symptoms may be migrainous in origin. Patients with BPPV-like symptoms but

repetitively normal positional tests may suffer from a predominantly positional form of vestibular migraine.

Chapter 7

Outline of future research

Otolith function testing (both in the form of rotational testing or evoked potential testing) has recently made it possible to understand some of the function of these end organs which has been less well known for long time. This is an exciting period of evolution of utricular function testing using two completely different techniques.

We found that the paradigm for unilateral centrifugation was very well tolerated both by normal and patients alike, when they were properly counselled for the technique beforehand. The paradigm used is slightly different to the one used by Clarke et al, 2003 with higher chair velocities and increased lateral translation of the rotating chair. This was done to generate higher gravito-inertial tilt, i.e. a stronger stimulus and thus hopefully more consistent results. Utricular function was studied in patients with common vestibular disorders, with special emphasis on Ménière's disease, as of all compartments of the inner ear the least understood in are the otoliths.

Each group with the more common vestibular disorders had small number of patients in them. The patients with vestibular neuritis did not show any consistent difference to normal controls but they might show a completely different picture when investigated during acute phase. However, there were a few patients who showed that both canal and utricular dysfunction can be persistent but, of interest, this does not seem to affect clinical recovery significantly. This finding is convergent with other studies (in our and other groups) that long term clinical outcome is a complex multi-factorial process involving psychological, visual and cortical processes (Cousins et al 2014; Palla et al, 2008)

It was interesting that BPPV patients did not show any change in utricular asymmetry even after an episode of acute vertigo which might point towards effective compensation

mechanisms in this group or that their own vertigo is stronger stimulus and does not affect their responses. Similarly, it can be postulated that the amount of otoconia released from the otoliths and which is responsible for the canalolithiasis may be very small. Hence the techniques used to detect a minor macular asymmetry may need to be far more sensitive. In this regard, it will be interesting to study using 3D electro-oculographic recordings which are more objective than SVV (Wuyts et al, 2003), especially in the BPPV group.

The larger Ménière's disease group showed significant utricular asymmetry and lower utricular gain when compared with normal, as expected from a panlabyrinthine disease. A novel finding was hearing loss can be a predictor of utricular asymmetry which can be accepted based on histopathological studies (Okuno and Sando, 1997). There was no significant correlation between symptomatology and end organ function which may point towards effective compensation. This raises the question whether otolith function compensates more effectively than canal function? Does utricular loss have any chronic implications? Further studies with larger number of patients along with correlation of symptoms, specific to utricular function, will be a step forward in gaining further insight into this interesting branch of vestibular science. Fortunately, since me finishing my research period and leaving the group, further patients have been recruited and, therefore, combining the two data sets will eventually present a better picture.

When examining the interaction between acute positional vertigo and visual dependence, in the final chapter, we serendipitously encountered an interesting group of patients with positional symptoms but testing negative on repeated Dix-Hallpike manoeuvres. They had higher baseline visual dependence which, unlike BPPV and control subjects, did not reduce on repeating the visual stimulation after the positional manoeuvres. On further analysis of the clinical group, it was unexpectedly found that they had a higher incidence of migraine compared to normal population. Hence, we speculated that this group might suffer from a

special type of vestibular migraine (positional vestibular migraine) and that some of their long term symptoms they exhibit may relate to maladaptive processes in visual dependency. In the future it will be useful to study utricular function in similar patients for two reasons. First, an alternative diagnosis to our 'positional vestibular migraine' may be a primary disorder of the otoliths and the UCF technique explored in this thesis would be a way forward here. Second, at least partly, the increased visual dependence in these patients may be due to reduced utricular function and, hence, the abnormalities in visual dependence we found would be of a peripheral (otolith) aetiology rather than central as expected in patients with vestibular migraine. Finally, and more generally, there are certain syndromes which interfere with day to day functioning like motion sickness, visual dependency, space and motion discomfort (Redfern et al, 2007) where future testing of the otolith function may help in further understanding and management.

Chapter 8

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Appendices

Appendix I: Dizziness Handicap Inventory (Jacobson and Newman, 1990)

Please answer Yes, No or Sometimes. Please note question relevant to **your dizziness only**.

1. Does looking up increase your problem?	Yes	Sometimes	No
2. Because of your problem, do you feel frustrated?	Yes	Sometimes	No
3. Because of your problem, do you restrict your travel for business or recreation?	Yes	Sometimes	No
3. Does walking down the aisle of a supermarket increase your problem?	Yes	Sometimes	No
4. Because of your problem, do you have difficulty getting into or out of bed?	Yes	Sometimes	No
5. Does your problem significantly restrict your participation in social activities such as going out to dinner, going to movies, dancing, or to parties?	Yes	Sometimes	No
6. Because of your problem, do you have difficulty reading?	Yes	Sometimes	No
7. Does performing more ambitious activities like sports, dancing, household chores such as sweeping or putting dishes away increase your problem?	Yes	Sometimes	No
8. Because of your problem, do you have difficulty reading?	Yes	Sometimes	No
9. Because of your problem, are you afraid to leave home without having someone with you?	Yes	Sometimes	No
10. Because of your problem, have you been embarrassed in front of others?	Yes	Sometimes	No
11. Do quick movements of your head increase your problem?	Yes	Sometimes	No
12. Because of your problem, do you avoid heights?	Yes	Sometimes	No
13. Does turning over in bed increase your problem?	Yes	Sometimes	No
14. Because of your problem, is it difficult for you to do strenuous housework or yard work?	Yes	Sometimes	No
15. Because of your problem, are you afraid people may think you are intoxicated?	Yes	Sometimes	No
16. Because of your problem, is it difficult for you to go for a walk by yourself?	Yes	Sometimes	No
17. Does walking down a sidewalk increase your problem?	Yes	Sometimes	No
18. Because of your problem, is it difficult for you to concentrate?	Yes	Sometimes	No
19. Because of your problem, is it difficult for you to go for a walk around your house in the dark?	Yes	Sometimes	No
20. Because of your problem, are you afraid to stay home alone?	Yes	Sometimes	No
22. Because of your problem, do you feel handicapped?	Yes	Sometimes	No
23. Because of your problem, are you depressed?	Yes	Sometimes	No
24. Does your problem interfere with your job or household responsibilities?	Yes	Sometimes	No
25. Does bending over increase your problem?	Yes	Sometimes	No

Appendix II: Tinnitus Handicap Inventory (Newman and Jacobson, 1996)

Please answer Yes, No or Sometimes. Please note question relevant to **your tinnitus only**.

1. Because of your tinnitus is it difficult for you to concentrate?	Yes	Sometimes	No
2. Does the loudness of your tinnitus make it difficult for you to hear people?	Yes	Sometimes	No
3. Does your tinnitus make you angry?	Yes	Sometimes	No
4. Does your tinnitus make you feel confused?	Yes	Sometimes	No
5. Because of your tinnitus do you feel desperate?	Yes	Sometimes	No
6. Do you complain a great deal about your tinnitus?	Yes	Sometimes	No
7. Because of your tinnitus do you have trouble falling to sleep at night?	Yes	Sometimes	No
8. Do you feel as though you cannot escape from your tinnitus?	Yes	Sometimes	No
9. Does your tinnitus interfere with your ability to enjoy social activities (such as going out to dinner, to the movies)?	Yes	Sometimes	No
10. Because of your tinnitus do you feel frustrated?	Yes	Sometimes	No
11. Because of your tinnitus do you feel that you have a terrible disease?	Yes	Sometimes	No
12. Does your tinnitus make it difficult for you to enjoy life?	Yes	Sometimes	No
13. Does your tinnitus interfere with your job or household responsibilities?	Yes	Sometimes	No
14. Because of your tinnitus do you find that you are often irritable?	Yes	Sometimes	No
15. Because of your tinnitus is it difficult for you to read?	Yes	Sometimes	No
16. Does your tinnitus make you upset?	Yes	Sometimes	No
17. Do you feel that your tinnitus problem has placed stress on your relationship with members of your family and friends?	Yes	Sometimes	No
18. Do you find it difficult to focus your attention away from your tinnitus and on to other things?	Yes	Sometimes	No
19. Do you feel that you have no control over your tinnitus?	Yes	Sometimes	No
20. Because of your tinnitus do you often feel tired?	Yes	Sometimes	No
21. Because of your tinnitus do you feel depressed?	Yes	Sometimes	No
22. Does your tinnitus make you feel anxious?	Yes	Sometimes	No
23. Do you feel that you can no longer cope with your tinnitus?	Yes	Sometimes	No
24. Does your tinnitus get worse when you are under stress?	Yes	Sometimes	No
25. Does your tinnitus make you feel insecure?	Yes	Sometimes	No

Appendix III: Vertigo symptom scale- short form (Yardley et al, 1992)

Please answer between 0-4 (0-never, 1- A few times, 2 several times, 3 quite often (every week), 4-very often (most days))

How often in the past month have you had the following symptoms?

1. A feeling that either you, or things around you, are spinning or moving, lasting less than 20 minutes
2. Hot or cold spells
3. Nausea (feeling sick), vomiting
4. A feeling that either you, or things around you, are spinning or moving, lasting more than 20 minutes
5. Heart pounding or fluttering
6. A feeling of being dizzy, disoriented or "swimmy", lasting all day
7. Headache, or feeling of pressure in the head
8. Unable to stand or walk properly without support, veering or staggering to one side
9. Difficulty breathing, been short of breath
10. Feeling unsteady, about to lose balance, lasting more than 20 minutes
11. Excessive sweating
12. Feeling faint, about to black out
13. Feeling unsteady, about to lose balance, lasting less than 20 minutes
14. Pains in the heart or chest region
15. A feeling of being dizzy, disoriented or "swimmy", lasting less than 20 minutes

Appendix IV: Functional Level Scale (AAO-HNS, 1995)

Regarding my current state of overall function, not just during attacks (check the ONE that best applies):

1-My dizziness has no effect on my activities at all.

2-When I am dizzy I have to stop what I am doing for a while, but it soon passes and I can resume activities. I continue to work, drive, and engage in any activity I choose without restriction. I have not changed any plans or activities to accommodate my dizziness.

3-When I am dizzy, I have to stop what I am doing for a while, but it does pass and I can resume activities. I continue to work, drive, and engage in most activities I choose, but I have had to change some plans and make some allowance for my dizziness.

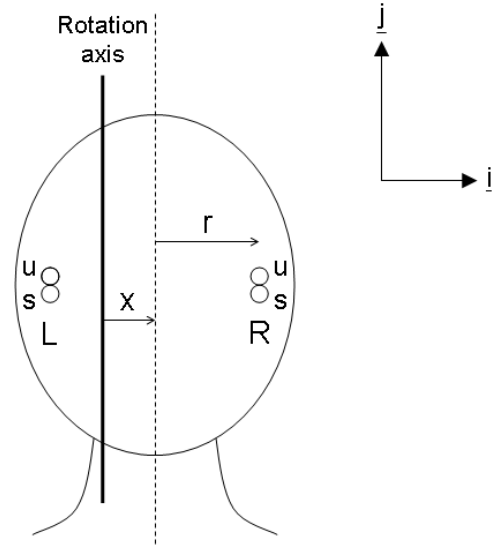
4-I am able to work, drive, travel, take care of a family, or engage in most essential activities, but I must exert a great deal of effort to do so. I must constantly make adjustments in my activities and budget my energies. I am barely making it.

5-I am unable to work, drive, or take care of a family. I am unable to do most of the active things that I used to. Even essential activities must be limited. I am disabled.

6-I have been disabled for 1 year or longer and/or I receive compensation (money) because of my dizziness or balance problem

Appendix V

UCF Analysis (after the formulation by Marv Faldon)



$$\underline{a}_R = -\omega^2 (r + x) \underline{i} + g \underline{j}$$

Acceleration at the left ear

$$\underline{a}_L = \omega^2 (r - x) \underline{i} + g \underline{j}$$

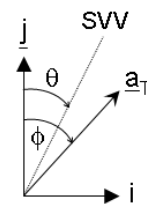
Define 'sensitivity' or 'weighting' of right/left utricles and saccules: U_R , U_L , S_R , S_L .

Maximum sensitivity = 1 (perfect transduction), minimum sensitivity = 0 (no function).

Assume that the utricles are only sensitive to horizontal accelerations ($\underline{i}$ -axis) and the saccules are only sensitive to vertical accelerations ($\underline{j}$ -axis); and that the net sensation of GIA is a weighted vector addition of the signals from each ear:

$$\underline{a}_T = -U_R \omega^2 (r + x) \underline{i} + S_R g \underline{j} + U_L \omega^2 (r - x) \underline{i} + S_L g \underline{j}$$

Tilt sensation angle = ϕ , SVV response angle = θ



Define SVV 'gain' factor (γ):

$$\tan \theta = \gamma \tan \phi$$

$$\tan \theta_c = \frac{\gamma \omega^2 (U_L - U_R) r}{g(S_L + S_R)}$$

Special case (1) – bilateral saccular dysfunction:

If both saccules are not working ($S_R = S_L = 0$) then the denominator in the expressions for the tangent of the SVV angle will be zero, giving an SVV angle of $\pm 90^\circ$ (unless the head is centred and the utricles are perfectly balanced). In this simple model, if the saccules are not contributing to the sensation of gravity, then any net horizontal (centripetal) acceleration sensed by the utricles will be used to estimate the direction of gravity. In reality, there are other proprioceptive cues to indicate upright, which will modify the subject's SVV response, but the SVV values could be large and unpredictable.

Special case (2) – complete bilateral utricular dysfunction:

If both utricles are not working ($U_R = U_L = 0$) then the SVV angle will not vary with head position ($m = 0$).

Other conditions:

In general, there should be a linear relationship between SVV angle and head displacement. When SVV angle is plotted against head position, the intercept (c) of the fitted line gives a measure of the utricular imbalance. The subjective 'gain' factor (γ) can be eliminated by comparing the intercept to the slope.

In the right eccentric position, $x = r$ and $\theta = \theta_R$

In the left eccentric position, $x = -r$ and $\theta = \theta_L$

In the central position, $x = 0$ and $\theta = \theta_C$

Least squares linear fit to 3 data points ($x = 0, \pm r$):

$$\text{Intercept} = (\theta_L + \theta_C + \theta_R) / 3$$

$$\text{Gradient} = (\theta_R - \theta_L) / 2r$$

Assuming $\tan \theta \approx \theta$ (small angle approximation).

$$\frac{\text{Intercept}}{\text{Gradient}} = \frac{2r(\theta_L + \theta_C + \theta_R)}{3(\theta_R - \theta_L)} = \frac{c}{m} = \frac{-(U_L - U_R)r}{(U_L + U_R)}$$

Define utricular asymmetry ('weakness', W):

$$W = \left(\frac{U_R - U_L}{U_R + U_L} \right)$$

$$W = \frac{2(\theta_L + \theta_C + \theta_R)}{3(\theta_R - \theta_L)} = \frac{(\text{mean_SVV})}{(\text{range_SVV})/2}$$

NB If the subject has a non-zero SVV setting in the static condition (with no chair rotation), then it may be assumed that this static value (θ_S) is added to each of the SVV values obtained during the high speed UCF test. In this case, the intercept should be corrected, giving a more general formula for the utricular weakness:

$$W = \frac{2(\theta_L + \theta_C + \theta_R - 3\theta_S)}{3(\theta_R - \theta_L)}$$

If there is a **complete LEFT unilateral utricular loss** ($U_L = 0$, $U_R \neq 0$), then **$W = +1$** .

In this case:

$$C = mr$$

$$\theta_L = 0$$

(or with a correction for the static SVV value: $\theta_L = \theta_S$). The SVV setting with the paretic left ear in the eccentric position would be the same as in the static condition – the only functioning utricle is on the rotation axis and so not subjected to any centripetal acceleration.

If there is a **complete RIGHT unilateral utricular loss** ($U_R = 0$, $U_L \neq 0$), then **$W = -1$** .

In this case:

$$C = -mr$$

$$\theta_R = 0$$

(or with a correction for the static SVV value: $\theta_R = \theta_S$). The SVV setting with the paretic right ear in the eccentric position would be the same as in the static condition – as before, the only functioning utricle is on the rotation axis and so not subjected to any centripetal acceleration.

If the lateral chair displacement (d) does not match the otolith eccentricity (r)

Least squares fit to measured data ($x = 0, \pm d$):

$$\text{Intercept} = (\theta_L + \theta_C + \theta_R) / 3$$

$$\text{Gradient} = (\theta_R - \theta_L) / 2d$$

$$\frac{\text{Intercept}}{\text{Gradient}} = \frac{2d(\theta_L + \theta_C + \theta_R)}{3(\theta_R - \theta_L)} = \frac{c}{m} = \frac{-(U_L - U_R)r}{(U_L + U_R)}$$

This gives a modified formula for the utricular weakness (W'):

$$W' = \left(\frac{U_R - U_L}{U_R + U_L} \right) = \frac{2d(\theta_L + \theta_C + \theta_R)}{3r(\theta_R - \theta_L)} = \frac{d}{r} \cdot \frac{(\text{mean}_{SVV})}{\frac{(\text{range}_{SVV})}{2}}$$

If there is a **complete LEFT unilateral utricular loss** ($U_L = 0, U_R \neq 0$), then **$W' = +1$** .

In this case, if the chair displacement (d) is smaller than the otolith eccentricity (r), then the mean SVV value (the intercept) will be greater than half the SVV range. Substituting the measured SVV values into the original formula for W (which assumes a chair displacement equal to otolith eccentricity) will give a 'weakness' value greater than 1. Similarly, if $d > r$ then the original W formula would produce an artifactually low 'weakness' value.

Therefore, a subject with strong utricular function asymmetry and otolith eccentricity larger than the 4cm chair displacement could have a measured utricular weakness above 100%.

SVV 'gain'

The range of SVV angles measured (radians):

$$\Delta\theta = \theta_L - \theta_R = -2mr = \frac{2\gamma\omega^2 r (U_L + U_R)}{g (S_L + S_R)}$$

$$\omega = 400\pi/180 \text{ rad/s}$$

$$r = 0.04 \text{ m}$$

$$g = 9.81 \text{ m/s}^2$$

If both utricles and saccules were acting as perfect transducers ($U = S = 1$), and the subject was able to set the SVV line exactly to the perceived gravitational vertical ($\gamma = 1$), then the range of SVV angles would be 22.8 deg ($\Delta\theta_p$).

The subjective gain factor (γ) is likely to be less than 1, which would reduce the measured range ($\Delta\theta_m$).

The measured range will also be affected by the relative sensitivity of the utricles and saccules. An SVV gain (G_{SVV}) could be defined by normalizing the measured range to the 'perfect' case:

$$G_{SVV} = \frac{\Delta\theta_m}{\Delta\theta_p} = \gamma \frac{(U_L + U_R)}{(S_L + S_R)}$$

UCF Experimental Predictions

1. In most cases, the UCF test should produce a characteristic pattern of SVV responses. During the high speed rotation, the SVV in the right eccentric position should be tilted CCW

compared to the SVV in the central position, and in the left eccentric position the SVV should be tilted CW compared to the SVV in the central position.

2. If the SVV does not vary with lateral chair position, then bilateral utricular loss is indicated.
3. The SVV during on-axis high speed chair rotation (θ_C) may be shifted with respect to the baseline static value (θ_S). A CW (+ve) shift of θ_C indicates right utricular loss, and a CCW (-ve) shift indicates left utricular loss.
4. In the case of a complete unilateral utricular loss, the SVV with the 'good' ear on-axis should be similar to the static value (as there will be no centripetal acceleration at the working utricle).
5. For a complete unilateral utricular loss, the mean shift in the SVV values, with respect to the static value, should be half of the maximum range. A mean shift greater than this could arise if the lateral displacement of the chair was smaller than the eccentricity of the subject's otoliths.
6. For a subject with balanced otolith function, the maximum range of SVV values ($\theta_L - \theta_R$) should be 22.8 deg. An SVV range larger than this could indicate a reduced saccular sensitivity. (The subject would be relying too heavily on the utricular sensations of acceleration for their perception of gravitational upright).
7. A non-typical pattern of SVV responses could indicate combined utricular and saccular dysfunction, or general subject confusion.