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VESTIBULAR FUNCTION IN DIFFERENT OTONEUROLOGICAL PATIENTS

AS MEASURED BY HEAD TILT AND HEAD IMPULSE TEST

Topi Jutila

ACADEMIC DISSERTATION

To be presented, with the permission of the Medical Faculty of the University of Helsinki, for public examination in the auditorium of the Department of Otorhinolaryngology – Head and Neck Surgery, Haartmaninkatu 4 E, on 5 September 2014, at 12 noon.

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ABSTRACT

Objectives
The first objective was to evaluate feasibility of head tilt testing and the motorized head impulse test (mHIT) for the quantification of vestibular function and its possible change in different otoneurological patient groups. The second objective was to compare these objective findings with symptoms and other signs for these patients.

Methods
Head tilt was measured by using a commercially available video-oculography (VOG) mask-integrated head position sensor in complete darkness in static and dynamic (subjective head vertical, SHV) conditions. The head tilt was measured in 20 healthy subjects, and in 30 patients with acute unilateral vestibular loss in the acute stage and at a mean of three months later. Head tilt was also measured in 43 patients with vestibular schwannoma preoperatively and at a mean of four months postoperatively.

The mHIT was used for quantifying the function of the horizontal angular vestibulo-ocular reflex (aVOR) in 30 patients with acute unilateral vestibular loss in the acute stage and at a mean of three months later. mHIT was also used to measure aVOR in 44 patients with cochlear implant (CI) preoperatively and at a mean of two months and 19 months postoperatively. The aVOR was assessed by gain and asymmetry in gain.

The patients completed a structured questionnaire during their visits to the vestibular laboratory to assess hearing, dizziness, and quality of life.

Results
Those patients with acute unilateral vestibular loss exhibited a slight head tilt towards the ipsilateral side, which significantly differed from that of controls, and which significantly recovered during the follow-up period. The mean head tilt in patients with VS was ipsilateral both pre- and postoperatively, and significantly larger than in controls. No significant change in head tilt after three months was encountered. In both patient groups the head tilt reinforced after returning from an ipsilateral head tilt.

In patients with acute unilateral vestibular loss, the initially low mean ipsilateral aVOR gain and high asymmetry improved significantly during the follow-up, whereas the contralateral gain remained normal and showed no significant change. During the follow-up visit a high symptom score correlated moderately with low gain and with high asymmetry. The preoperative aVOR was deficient in the majority of the CI recipients. The

mean gain or asymmetry showed no significant change postoperatively. The ipsilateral gain decreased during the postoperative period in four (10%) individual CI patients.

Conlusions

Evaluation of head tilt and the underlying utricular function is possible with commercial VOG equipment including an integrated head position sensor. A slight head tilt towards the side of the lesion in patients with acute unilateral vestibular loss usually improves, but no significant long-term change was seen in patients with VS after surgery. Head tilting was pronounced after returning from an ipsilateral head tilt.

The mHIT is able to detect acute unilateral vestibular loss in most patients as a clear asymmetry in their respective high-frequency aVOR gain, which usually resolves in a few months. Patients with low gain and high asymmetry after a few months may benefit from follow-up and more aggressive rehabilitation. The decrease of the horizontal VOR function is a possible but rare complication of cochlear implantation, which should be taken into account in patient counselling especially when planning bilateral cochlear implantation.

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Topi Jutila

CONTENTS

ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I **Hirvonen TP, Jutila T, Aalto H**
Subjective head vertical test reveals subtle head tilt in unilateral peripheral vestibular loss
Eur Arch Otorhinolaryngol 2011;268:1523-6

II **Jutila T, Aalto H, Hirvonen TP**
Recovery of the horizontal vestibulo-ocular reflex in motorized head impulse test is common after vestibular loss
Acta Otolaryngol 2012;132:726-31

III **Jutila T, Aalto H, Hirvonen TP**
Cochlear implantation rarely alters horizontal vestibulo-ocular reflex in motorized head impulse test
Otol Neurotol 2013;34:48-52

IV **Jutila T, Aalto H, Hirvonen TP**
Head tilt is pronounced after an ipsilateral head roll in patients with vestibular schwannoma
Eur Arch Otorhinolaryngol 2014;271:1791-6.

The publications are referred to in the text by their roman numerals.

ABBREVIATIONS

3D-VOG	three-dimensional video-oculography
aVOR	angular vestibulo-ocular reflex
CI	cochlear implant
cVEMP	cervical vestibular-evoked myogenic potential
EOG	electro-oculography
HIT	head impulse test
lVOR	linear vestibulo-ocular reflex
mHIT	motorized head impulse test
oVEMP	ocular vestibular-evoked myogenic potential
SCC	semicircular canal
SD	standard deviation
SHV	subjective head vertical
SVH	subjective visual horizontal
SVV	subjective visual vertical
VEMP	vestibular-evoked myogenic potential
VN	vestibular neuritis
VOG	video-oculography
VOR	vestibulo-ocular reflex
VS	vestibular schwannoma

1 INTRODUCTION

The vestibular system maintains balance and spatial orientation, and keeps vision stable during motion. Damage to the vestibular system leads to vertigo or dizziness, usually due to the asymmetry of the vestibular input between the right and left vestibular nuclei in the brainstem.

Vestibular neuritis (VN) causes a sudden unilateral loss of vestibular function, which leads to symptoms such as vertigo, postural imbalance, and nausea (Brandt et al. 2010). Up to half of cochlear implant (CI) recipients exhibit vestibular symptoms before surgery, and balance disturbances are also common after the CI surgery (Ito 1998, Kubo et al. 2001, Steenerson et al. 2001, Fina et al. 2003, Basta et al. 2008, Todt et al. 2008, Krause et al. 2009). Most of the patients with vestibular schwannoma (VS) experience disequilibrium, which becomes at least temporarily more prevalent postoperatively (Saman et al. 2009).

The vestibular organ comprises three semicircular canals (SCCs) and two otolithic organs, the utricle and the saccule, on each side. The vestibulo-ocular reflex (VOR) co-ordinates eye movements during head motion in order to keep the retinal images stable. The SCCs sense angular acceleration and produce the angular vestibulo-ocular reflex (aVOR), which involves a three-neuron reflex arc that connects the SCCs and the extraocular muscles.

The most common method for quantifying the aVOR function has been the caloric test. The head impulse test (HIT) allows the evaluation of the VOR in physiological stimulation frequencies by utilizing brisk head rotations (Halmagyi and Curthoys 1988). The HIT can be used as a bedside test or as a quantitative test (Halmagyi 2005, Cnyrim et al. 2008, Newman-Toker et al. 2008). Manually delivered head impulses that use magnetic scleral search coils for monitoring eye and head motion have been the gold standard for the quantitative HIT, albeit they are invasive and demanding upon resources (Halmagyi et al. 1990b). The motorized head impulse rotator was introduced for quantitative evaluation of the horizontal aVOR responses to achieve uniform high-acceleration head impulses (Aalto et al. 2002).

A sudden unilateral loss of utricular function causes the ocular tilt reaction, which comprises head tilt, ocular torsion, and ocular skew deviation towards the lesioned side (Halmagyi et al. 1979). Utricular function has been assessed indirectly with subjective visual horizontal or vertical (SVH/SVV) tests (Tabak et al. 1997a, Min et al. 2007), which primarily reflect the ocular torsion that derives from the asymmetry of the utricular input between the right and left vestibular nuclei (Curthoys et al. 1991b). We applied a direct

method to quantify head tilt with video-oculography (VOG) equipment including a head position sensor to bring additional value to the assessment of the utricular function.

The aim of this study was to assess vestibular function and its possible change by 1) quantitatively measuring head tilt in patients with VN and VS, and 2) quantifying motorized head impulse test (mHIT) responses in patients with VN and patients who have received a CI.

2 REVIEW OF THE LITERATURE

2.1 ANATOMY AND PHYSIOLOGY OF THE VESTIBULAR SYSTEM

2.1.1 PERIPHERAL VESTIBULAR SYSTEM

The peripheral part of the vestibular system comprises the labyrinth, which lies in the petrous portion of the temporal bone. It comprises five end organs: the horizontal, superior and posterior SCCs, and the otolithic organs (the utricle and saccule).

Two types of sensory neuroepithelia exist in the vestibular system: the macula in the otolithic organs, and the crista ampullaris in the SCCs. The neuroepithelia are located in the endolymph-filled membraneous labyrinth. The neuroepithelium contains two types of hair cells, globular-shaped type I hair cells, and cylindrical type II hair cells. On the apical end of each hair cell lie 70-100 stereocilia, which increase in height towards the thicker and longer kinocilium. Tip-links connect the tips of the stereocilia. The tip links open and close mechanosensory channels, which results in the depolarization or hyperpolarization of the hair cell depending on the direction of the head motion. For instance when the stereocilia tilt towards the kinocilium, the hair cell depolarizes (excitation), and when the stereocilia bend in the opposite direction, the hair cell hyperpolarizes (inhibition) (Khan and Chang 2013).

The SCCs lie in approximately 90° angle towards each other so that the SCCs are able to sense angular acceleration in three planes: yaw, pitch, and roll. The superior and the posterior SCC lie in approximately 45° angle to the sagittal plane, and the horizontal SCC approximately 20° upwards towards the axial plane (Della Santina et al. 2005). Each SCC has a parallel canal on the contralateral side that acts as the complementary half of the pair so that when one canal excites, the other canal inhibits. The horizontal SCCs are paired, and the superior SCCs pair with the contralateral posterior SCCs. The anterior opening of the horizontal and superior canal and the inferior opening of posterior canal dilates to form the ampulla (Figure 1). The hair cells lie on the surface of the crista, and their cilia are embedded through a gelatinous mass called the cupula, which reaches from the crista to the ceiling of the ampulla, thereby plugging it. The orientation of the hair cells in each crista is uniform so that all the kinocilia of the superior and posterior canals are oriented towards the duct, and the kinocilia of the horizontal canal are oriented towards the vestibule (Baloh and Kerber 2011a).

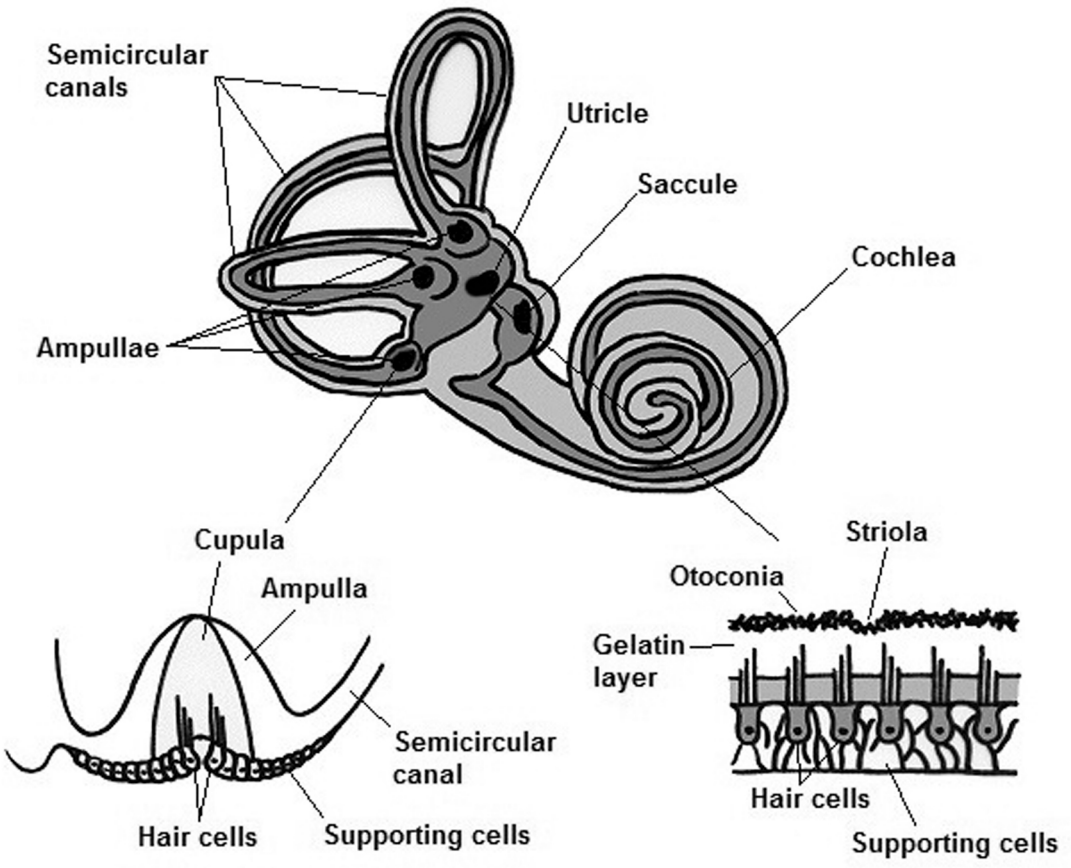

Figure 1 Overview of the peripheral vestibular system with the ampulla, and the macula of the otolithic organs enlargened.

The utricle and saccule are located in the vestibule. The macula of the utricle mostly lies in the horizontal plane, and in the saccule lies mostly in the sagittal plane. Thus, the utricle senses predominantly horizontal acceleration and tilting of the head, and the saccule senses mostly vertical acceleration, most importantly gravitational acceleration. The macula is covered with a gelatinous otolithic membrane, which contains small calcium carbonate particles, otoliths, or otoconia, on the surface. The stereocilia protrude into the otolithic membrane. The stereocilia are oriented according to the striola, a curved zone that divides the macula: the kinocilia in the utricle are towards the striola, and away from the striola in the saccule. The density of the otolithic membrane is greater than the surrounding endolymph because of the otoconia. Therefore, linear acceleration results in otolithic membrane displacement, causing a bending of the cilia. Because of the orientation of the hair cells, motion produces excitation in one part of the hair cells while inhibiting the other part (Rask-Andersen and Bagger-Sjöbäck 2008).

The nerves from the utricle, horizontal and superior SCCs, and nerve fibres from the anterosuperior portion of the saccule comprise the superior division of the vestibular nerve. The nerve from the posterior SCC and the majority of the nerve fibres from the saccule form the inferior division. The cell bodies are gathered in the vestibular ganglion, or Scarpa's ganglion, which is located in the lateral portion of the internal auditory meatus (Figure 2). The vestibular nerve constitutes the vestibulocochlear nerve together with the cochlear nerve. This VIII cranial nerve travels through the internal auditory canal along with the facial nerve (Khan and Chang 2013).

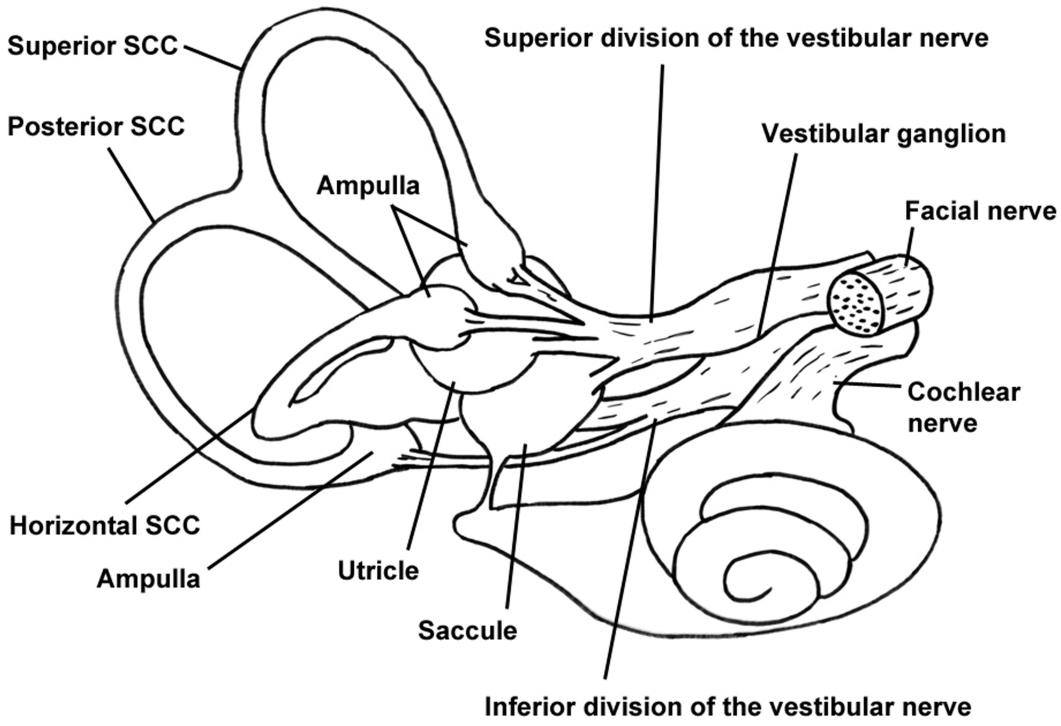

Figure 2 Neural connections from the superior and inferior division of the vestibular nerve.

2.1.2 CENTRAL VESTIBULAR SYSTEM

Afferents from the ipsilateral SCCs and otolithic organs project to four vestibular nuclei in the brainstem: the medial, superior, lateral, and inferior vestibular nucleus. The vestibular nuclei further connect with the motor nuclei of the extraocular muscles, the cerebellum, and the descending spinal cord. The vestibular nuclei receive visual and proprioceptive signals in addition to the primary vestibular signals (Angelaki and Cullen 2008).

The ascending efferents from the medial vestibular nucleus project via the medial longitudinal fasciculus to the motor nuclei of the extraocular muscles and supply the VOR. The medial vestibular nucleus also controls the vestibulospinal reflex via descending projections in the medial vestibulospinal tract to the cervical spinal cord. The efferents from the

superior vestibular nucleus also project to the extraocular motor nuclei via the medial longitudinal fasciculus to control the VOR. The efferents from the lateral vestibular nucleus constitute the lateral vestibular tract in the lateral spinal cord, which serves as a part of the vestibulospinal reflex in the trunk and limbs. The inferior vestibular nucleus has efferent projections with the other vestibular nuclei, and the cerebellum (Khan and Chang 2013).

The cerebellum monitors the vestibular input, and calibrates and co-ordinates the head and eye movements. This includes the VOR and the cerebellum also regulates the vestibulospinal reflex (Walker and Zee 2005, Baloh and Kerber 2011a). The vestibulospinal reflex involves complex neural connections to keep head and body stable in space, thus measuring it is nonspecific, insensitive, and is subject to various sources of distraction (Kingma et al. 2011).

The location of the vestibular cortex remains unresolved, and the cortical vestibular connections are not clearly understood, but the parieto-insular cortex is thought to be at the centre of the vestibular cortical network (Baloh and Kerber 2011a). Vestibular connections are also thought to exist in the thalamus and the hippocampus. It is believed that the hippocampus processes spatial orientation and memory (Muir et al. 2009, Lopez and Blanke 2011).

2.2 VESTIBULO-OCULAR REFLEXES

2.2.1 ANGULAR VESTIBULO-OCULAR REFLEX

The aVOR stabilizes gaze during head rotation by inducing compensatory eye movements, or the slow phase of nystagmus, opposite in direction to the movement of the head (Figure 2). Nystagmus appears in the plane of the stimulated SCC (Ewald 1892). For example, the horizontal canals stimulate during horizontal head rotation, and the resulting nystagmus is horizontal. The same direction-dependency also applies to peripheral pathological nystagmus that is derived from the pathologies in the SCCs. During natural head motions, however, all of the SCCs are usually stimulated (Carey and Della Santina 2005).

The shortest pathway of the aVOR comprises a three-neuron reflex arc. The primary afferent connects the hair cells with the vestibular nuclei in the brainstem. The interneurons connect the vestibular nuclei with the motor nuclei of the III (oculomotor), IV (trochlear), and VI (abducens) cranial nerves. The motoneuron connects the motor nuclei with the extraocular muscles (Baloh and Kerber 2011a). The excitatory impulses transmit via the

medial longitudinal fasciculus to the oculomotor nuclei, and via the ascending tract of Deiters to the abducens nuclei.

Angular acceleration causes motion in the surrounding endolymph, which results in displacement of the cupula and de- or hyperpolarization of the hair cells. The endolymph flow towards the ampulla is called ampullopetal, and the flow away from the ampulla is called ampullofugal. The afferent nerve fibres of the horizontal canals excite during ampullopetal flow, whereas the afferent fibres of the vertical canals (superior and posterior canals) excite during ampullofugal flow (Baloh and Kerber 2011a). Thus, during rapid head rotation, the SCC on the side of the rotation excites, and the opposite parallel SCC inhibits. However, the excited SCC produces a larger response than its paired counterpart (Ewald 1892, Halmagyi et al. 1990a). This is due to inhibitory cutoff (Halmagyi et al. 1990b, Weber et al. 2008). At rest, the vestibular fibres in mammals have a spontaneous firing rate of 50 to 100 spikes per second (Goldberg 2000). During motion, the firing rate on the inhibitory side can decrease to no lower than zero, while on the excitatory side the firing rate can multiply to 300 to 400 spikes per second. This directional asymmetry results in the aVOR and the compensatory eye movements that are induced mainly by the SCC on the excitatory side, which is also known as Ewald's second law.

The most common parameters for defining aVOR are gain, asymmetry in gain, and latency. The gain is the ratio of the eye to the head angular velocity. A normative gain is thus close to unity (Tabak and Collewijn 1994, Aw et al. 1996b, Hirvonen et al. 2007), when the eyes rotate at the same velocity as the head, but in the opposite direction. The VOR can produce a gain close to unity up to a head velocity of 350°/s, but at higher velocities the gain saturates (Pulaski et al. 1981, Roy and Tomlinson 2004). Weber et al. (2008) measured gain in normal subjects by using different head accelerations, and found that the maximum gain of 1.02 was reached at about 1700°/s², after which the gain slowly decreased as head acceleration increased. Voluntary head-on-body rotations can reach velocity of 800°/s, but head velocities during natural locomotion do not reach the saturation limit of the VOR (Grossman et al. 1988, Grossman et al. 1989). The asymmetry in gain between right and left side is calculated by the following equation: ([gain right – gain left] / [gain right + gain left]) x 100%. In healthy subjects, the asymmetry was reported to range between 0 and 6% (Schmid-Priscoveanu et al. 2001, Park et al. 2005, Weber et al. 2008). The latency, defined as the time from the beginning of the head movement to the onset of the eye movement, ranges in healthy subjects from 3 to 9 ms (Tabak and Collewijn 1994, Aw et al. 1996b, Collewijn and Smeets 2000, Hirvonen et al. 2007).

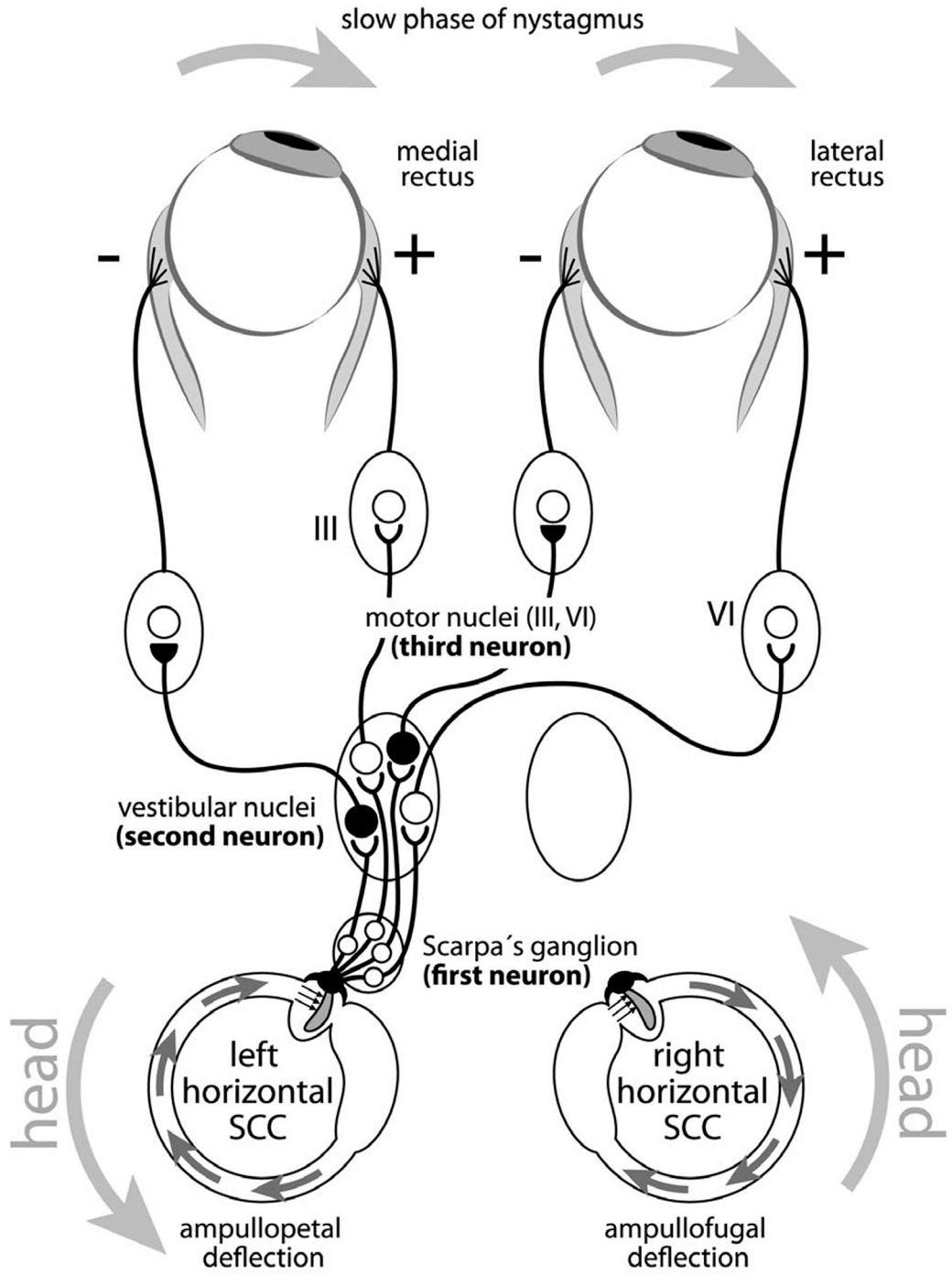

Figure 3 Neural pathways of the horizontal aVOR. Head rotation to the left generates endolymph flow towards the ampulla of the left horizontal SCC (excitation), and away from the ampullaa of the right horizontal SCC (inhibition). The excitatory interneurons from the vestibular nuclei connect to the motor neurons of the ocular motor nuclei (III and VI), which results in turning the eyes to the right (opposite to the direction of head turn). The inhibitory interneurons cause relaxation of the antagonist eye muscles, which augments the eye movement. Reproduced with permission of the copyright owner.

2.2.2 INTERACTIONS OF THE ANGULAR VESTIBULO-OCULAR REFLEX

Three oculomotor systems apart from the aVOR produce compensatory eye movements: the saccadic, smooth pursuit, and optokinetic systems interact with the vestibular system to stabilize the gaze (Baloh and Kerber 2011a). The saccadic system produces a rapid eye movement (a saccade) from one target to another. The smooth pursuit system maintains gaze on a moving target. The optokinetic reflex responds to the motion of the entire visual field to produce corrective saccades within eye tracking motion. The vision-based oculomotor systems function best at low-frequency and slow head motions, and they have a substantially longer latency, 70-80 ms at shortest, compared to that of the VOR (Collewijn and Smeets 2000). The VOR is necessary for gaze stabilization during rapid head movements, because vision based systems are insufficient for many natural head movements (Hain et al. 1987). For example, during running, the head can reach velocities of 90°/s and harmonics of 20 Hz (Grossman et al. 1988, Grossman et al. 1989).

The cervico-ocular reflex is induced by the neck proprioceptors, and alongside the VOR and the oculomotor systems, it takes part in stabilizing the gaze. In animal studies, displacing the body about a fixed head has produced compensatory eye movements (Gresty 1976). Interactions of the cervico-ocular reflex and the VOR are challenging to study because voluntarily and visually controlled eye movements are dominant, and because the gain of the cervico-ocular reflex is considerably lower than that of the VOR. Moreover, the cervico-ocular reflex seems to have a minor effect on gaze stability in primates (Schubert et al. 2004a).

2.2.3 PATHOPHYSIOLOGY OF THE ANGULAR VESTIBULO-OCULAR REFLEX

In unilateral vestibular deficit, the aVOR system may fail to supply compensatory eye movements. The magnitude of symptoms and signs depends on the time span in which the deficit occurs, the extent of the deficit, and whether the deficit is uni- or bilateral (Baloh and Kerber 2011a). After acute unilateral vestibular loss, such as that occurs in VN or vestibular nerve deafferentation, signs such as spontaneous horizontal-rotatory nystagmus beating towards the healthy side manifest. The often severe symptoms of acute unilateral vestibular loss are due to the sudden imbalance of the baseline activity of the ipsilateral and the contralateral vestibular nerve (Baloh 2003). In bilateral vestibular loss, patients often experience no vertigo, but do experience oscillopsia or visual blurring during head motion, and instability, especially in darkness and on uneven surfaces, due to loss of the VOR and vestibulospinal reflex (Kim et al. 2011). In slowly progressive unilateral vestibular deficits as in VS, the symptoms are often milder because

central compensation occurs concurrently with the vestibular function decrease (Uehara et al. 2011).

In the acute stage after unilateral vestibular deficit, the ipsilateral aVOR gain is decreased and the lesioned vestibular organ is unable to provide fully compensatory eye movements. The gain also decreases slightly on the contralateral side due to a normal aVOR requiring contribution of both SCCs (Halmagyi et al. 1990a, Weber et al. 2008), although the SCC on the side of the head rotation predominantly drives the aVOR, as previously described. Allum and Ledin (1999) found that the gain in low-acceleration rotational chair test normalized within several weeks after the onset of VN. In the same study, the caloric response normalized in 34% of the patients within four months. Schmid-Priscoveanu et al. (2001) found that the caloric response became symmetrical in 36% of the patients, who were measured at least two months after the onset of VN. Their finding was in accordance with that of Kammerlind et al. (2006), who found that 33% of the patients showed a normal caloric response 10 weeks after VN. In contrast, Mandala and Nuti (2009) found 63% of VN patients to have an abnormal caloric response even at five years after VN. Choi et al. (2007) reported 47% of patients with VN to still have severe caloric paresis even at one year after VN, whereas the bedside HIT was abnormal in 30% of the patients after one year. After unilateral vestibular deafferentation and after VS surgery, the ipsilateral gain as measured by high-frequency quantitative HIT was reported to be permanently decreased (Halmagyi et al. 1990a, Halmagyi et al. 1990b, Aw et al. 1996a, Halmagyi et al. 2003, Weber et al. 2008, Hirvonen et al. 2008, Batuecas-Caletrio et al. 2013). The high-frequency horizontal VOR gain after VN has been found to significantly improve over time (Palla and Straumann 2004), although other data also show a permanently decreased gain (Schmid-Priscoveanu et al. 1999, Schmid-Priscoveanu et al. 2001).

Few data exist on quantitative high-frequency HIT in patients who have received CI. Migliaccio et al. (2005), and Melvin et al. (2009) respectively found 1 of 11, and 1 of 28 CI ears to have reduced postoperative function compared to preoperative, for the high-frequency HIT. More data exist on the caloric test in CI patients. Even preoperatively, 28 to 36% of the CI ears have been found to be hypo- or areflexic in the caloric test (Vibert et al. 2001, Buchman et al. 2004, Melvin et al. 2009, Krause et al. 2009, Wagner et al. 2010). Postoperative caloric response has further decreased between 6 to 41% of the CI ears (Brey et al. 1995, Ito 2008, Buchman et al. 2004, Melvin et al. 2009, Krause et al. 2009, Wagner et al. 2010).

2.2.4 OTOLITH-OCULAR REFLEXES

Otolithic organs sense linear acceleration due to the translational motion of the head and also to head tilt with respect to gravity: in response these

organs generate compensatory eye movements by the linear vestibulo-ocular reflex (lVOR). Unlike the aVOR, lVOR is strongly modulated by the viewing distance: a distant target requires less compensatory eye movement than a close target during a translation of the head (Paige 2002). The aVOR stabilizes images on the entire retina, but the lVOR stabilizes images on only one spatial location in the visual field, usually the fovea. The lVOR cooperates with smooth pursuit and vergence systems, which also stabilize foveal images (Angelaki and Hess 2001). The ocular tilt reflex produces ocular counterrolling and skewing when the head is tilted in the roll plane. This is mainly due to excitation of the utricle on the side of the tilt (Baloh and Kerber 2011a). Otolithic organs-induced nystagmus is challenging to apply to diagnostics because the gain of the torsional eye movements is minor and variable (Schworm et al. 2002, Zingler et al. 2006). During sustained head roll, the ocular counterroll compensates only about 10—20% of the head roll (Miller 1962, Diamond and Markham 1981, Schworm et al. 2002, Zingler et al. 2006).

A sudden unilateral loss of utricular function causes the ocular tilt reaction that comprises head tilt, ocular torsion, and skew deviation (the pupil on the intact side is elevated and the pupil on the lesioned side is depressed) towards the lesioned side (Halmagyi et al. 1979). The ocular torsion at one week after unilateral vestibular neurectomy has been reported to be about 10°, which resolves to 3° within a few months (Curthoys et al. 1991a). The perceived visual surroundings in SVH/SVV test deviate towards the lesioned side. After sudden unilateral vestibular deficit the deviation of SVH/SVV has varied between 2 to 10°, and in most patients the deviation has improved rapidly (Tabak et al. 1997a, Min et al. 2007, Choi et al. 2007, Kim et al. 2008). After vestibular neurectomy the SVH/SVV also improves over time compared to the immediate postoperative result, but usually it remains permanently deviated to a certain extent (Böhmer and Rickenmann 1995). Ogawa et al. (2010) reported that after ear surgery excluding the removal of VS, no significant deviation in SVV occurred in most patients. Those authors also noted that in those patients whose SVV deviated, the deviation was more often towards the healthy side.

Vestibular-evoked myogenic potential (VEMP) testing in VN patients helps to distinguish whether the superior or inferior vestibular nerve is affected, or whether both are affected: for example, the cervical VEMP (cVEMP) response is usually normal while the ocular VEMP (oVEMP) is abnormal in superior vestibular neuritis. The former reflects mainly the inferior vestibular nerve function and the latter the superior vestibular nerve function (Rosengren and Kingma 2013). The cVEMP response seems to improve within a few weeks after VN, and otolithic function in general seems to improve more rapidly compared to semicircular canal-related test

abnormalities (Kim et al. 2008). The cVEMP is abnormal in 55—80% of patients with VS (Baloh and Kerber 2011b).

2.3 VESTIBULAR NEURITIS

The VN causes acute unilateral loss of vestibular function, which leads to symptoms and signs such as vertigo, postural imbalance, nausea, and horizontal-rotatory spontaneous nystagmus with fast phases towards the unaffected ear (Brandt et al. 2010). The incidence of the VN is unclear: a Japanese survey based on questionnaires suggests a frequency of 3.5 per 100 000 persons per year (Sekitani et al. 1993), but this figure is probably underestimated (Neuhauser 2007). The aetiology of the VN is suggestive to be the reactivation of a latent herpes simplex type 1 virus infection in the Scarpa's ganglia, although no conclusive proof of this exists (Strupp and Brandt 2012). The VN may affect both branches of the vestibular nerve, but sometimes only the superior and less frequently only the inferior vestibular nerve (Fetter and Dichgans 1996, Aw et al. 2001, Halmagyi et al. 2002). Treatment using methylprednisolone improves the long-term outcome of the peripheral vestibular function (Strupp et al. 2004). The effect of methylprednisolone on symptoms is, however, unknown. Symptoms and signs usually recover gradually and almost completely over several weeks to months. This results from a combination of central compensation (Baloh 2003), and the recovery of the peripheral vestibular function, which is often incomplete (Schmid-Priscoveanu et al. 2001, Halmagyi et al. 2010). Persisting symptoms have, however, been reported in up to half of the VN patients even years after contracting it (Godemann et al. 2005, Kammerlind et al. 2005).

2.4 VESTIBULAR SCHWANNOMA

VS is a benign slow-growing cerebellopontine angle tumour that arises from the Schwann cells of the vestibular nerve in the internal auditory canal. VSs are rare: the incidence is approximately 1 per 100 000 persons per year (Propp et al. 2006). The most common symptom in VS patients is a slowly progressive unilateral hearing loss, and the other common symptoms are tinnitus and disequilibrium (Mattox 1987, Mann and Gouveris 2009). Treatment options for VS comprise serial observation, radiotherapy, and microsurgery (Phillips et al. 2010).

Surgical treatment for VS usually impairs both hearing and the vestibular function ipsilaterally, the latter causing temporary worsening of disequilibrium. According to a review by Saman et al. (2009), 50 to 69% of VS patients experience disequilibrium before VS surgery and 72 to 90% after

surgery. The disequilibrium, however, usually ameliorates within a few months postoperation. According to Wiegand et al. (1996), 9% of VS patients complain of persistent gain instability one year postoperatively. The variation in frequency and duration of the postoperative disequilibrium, however, is considerable between studies. According to a survey based on postal questionnaires, 56% of patients experienced dizziness at six months postoperation (Parving et al. 1992). Driscoll et al. (1998) reported after a retrospective medical records review that 31% of VS patients had disequilibrium that lasted more than three months postoperation. Different study settings and possibly different definitions of disequilibrium or dizziness most likely explain the different symptom rates. A later study by Lynn et al. (1999) used structured questionnaires, partly with the same patients as in the abovementioned study by Driscoll et al. (1998), and found that 65% of the patients had recently experienced dizziness even at four years after surgery.

2.5 COCHLEAR IMPLANTATION

Cochlear implantation is currently the method of choice for the rehabilitation of patients with severe-to-profound hearing impairment. The first CI was implanted by otologist William House and neurosurgeon John Doyle in 1961 (Mudry and Mills 2013). Improvements in the design of the implant and the surgery have widened the indication criteria. The CI includes (a) microphone, (b) speech processor that sends the processed electrical sound signal to the (c) transmitter that transmits the signals across the skin to the implanted (d) receiver and stimulator that sends the electric impulses to the (e) the electrode array that stimulates the auditory nerve fibres. The surgery includes cortical mastoidectomy followed by posterior tympanotomy. The bed for the receiver/stimulator is prepared on the skull. The electrode array is inserted into the cochlear scala tympani either via a separate cochleostomy anteroinferior of the round window or via the round window membrane (Adunka et al. 2004, Skarzynski et al. 2011).

Electrode insertion into the cochlea usually leads to a certain degree of trauma in the proximity of the electrode. Histopathology studies have shown damage to the spiral ligament, stria vascularis, and the organ of Corti in the basal turn of the cochlea in most implanted ears (Linthicum et al. 1991, Fayad et al. 1991, Fayad and Linthicum 2006). Damage in the vestibular end organs has also been seen in most implanted ears (Tien and Linthicum 2002, Handzel et al. 2005). The damage to the vestibular end organs and primary vestibular neurons in cochlear implantation can be caused by direct damage, inflammatory response, disturbance of the homeostasis of fluid spaces, or other disruptive mechanisms (Handzel et al. 2005). No relationship between histopathological changes and any vestibular symptoms or auditory

performance with the implant has been found, however (Tien and Linthicum 2002, Fayad and Linthicum 2006).

Vestibular symptoms occur in up to 51% of CI patients even preoperatively (Steenerson et al. 2001, Fina et al. 2003, Basta et al. 2008, Todt et al. 2008). After cochlear implantation, vestibular symptoms have occurred in 39 to 74% of the patients (Ito 1998, Kubo et al. 2001, Steenerson et al. 2001, Fina et al. 2003, Todt et al. 2008, Krause 2009). Enticott et al. (2006) found 32% of the CI patients to have poorer postoperative Dizziness Handicap Inventory scores compared to the preoperative phase. In the study by Fina et al. (2003), 55% of the CI patients who were dizzy postoperatively had experienced no preoperative dizziness. On the other hand, 20% of the preoperative dizzy patients had no postoperative dizziness. Another study with both pre- and postoperative assessment of vertigo was conducted by Todt et al. (2008), in which the proportion of patients who experienced vertigo increased from the preoperative value of 45% to 53% at six to eight weeks postoperatively.

2.6 CLINICAL EXAMINATION OF ANGULAR VESTIBULO-OCULAR REFLEXES

2.6.1 EXAMINATION OF PATHOLOGICAL NYSTAGMUS

Nystagmus is often defined as an involuntary rhythmic oscillation of the eyes. Peripheral pathological nystagmus consists of slow phases that represent eye movement signals. They also represent fast phases that are usually more obvious to notice, although they indicate resetting actions that bring the pupil back to the centre and are not vestibular organ-induced. The direction of nystagmus is by convention defined as the direction of the fast phase (Hullar et al. 2005, Baloh and Kerber 2011b).

The evaluation of pathological nystagmus covers the spontaneous and provoked (changes in gaze fixation, eye position, and head position) nystagmus. Peripheral pathological nystagmus is suppressed by visual fixation. Frenzel glasses with about +20—30 dioptre lenses partially prevent fixation and make the eyes easily visualized (Hirvonen et al. 2012). VOG goggles allow more sensitive evaluation of nystagmus with total prevention of fixation with an eye cover. The effect of fixation can be tested allowing the patient to fixate either on the visual surroundings or VOG goggles-integrated light (Hirvonen and Aalto 2009). The effect of the eye position can be examined with the patient fixating on a target 20—30° to the left, right, up, and down. Extreme eye positions should be avoided because they may elicit physiological end-point nystagmus (Baloh and Kerber 2011b). Peripheral nystagmus strengthens on gaze towards the fast phase and suppresses on gaze away from the fast phase, which is known as Alexander's law (Robinson

et al. 1984). Head-shaking nystagmus is evaluated by turning the patient's head 20—30 times rapidly (1—2 Hz) in the horizontal plane. This may elicit several beats of nystagmus after the spontaneous nystagmus has resolved, because of a remaining asymmetry in the velocity-storage mechanism in the brainstem (Brandt and Strupp 2005). Positional nystagmus, as in benign paroxysmal positional vertigo, can be provoked by the Dix-Hallpike test for the posterior SCC, and also by the supine positional test for the horizontal SCC.

In patients with perilymph fistula or SCC dehiscence, nystagmus and vertigo may be induced by pressure changes to the middle ear or by sound (Brandt and Strupp 2005).

2.6.2 BEDSIDE HEAD IMPULSE TEST

The doll's eye test (oculocephalic response) is a useful test of the VOR in comatose patients only since their visuomotor system is not functioning (Leigh et al. 1984).

The HIT was first described by Halmagyi and Curthoys (1988) whereby a brief, passive, small-amplitude (10—20°), high-acceleration, unpredictable head thrusts applied by the examiner. A normal subject is able to maintain fixation of the eyes on a target, usually the examiner's nose, because the VOR drives the eyes to compensate for the head motion (Carey and Della Santina 2005). So-called catch-up saccades (eyes moving first with the head, followed by corrective saccadic eye movements towards the target) are a sign of an insufficient VOR on the side of the head movement. The horizontal SCC is the most feasible to examine, although the HIT can be performed for all SCCs (Curthoys 2012). The sensitivity of the HIT can be enhanced by applying the head thrusts unpredictably in time and direction, and keeping the head in 20° cervical flexion (Schubert et al. 2004b). The HIT allows testing for high-acceleration, high-frequency motions, the pathology of which can significantly differ from low-frequency losses revealed by the caloric test (Hullar et al. 2005).

2.6.3 COLD CALORIC TEST

Ice water irrigation of the ear canal is applicable for bedside assessment of the horizontal SCC function. Ice water induces horizontal nystagmus beating towards the opposite ear, but in the case of a non-functioning SCC and its nerve afferents (Coats and Smith 1967), nystagmus is not induced. In normal subjects the duration and speed of the induced nystagmus varies, but an asymmetry of > 20% in duration of the nystagmus may indicate pathology on the side of the weaker response. The HIT has widely replaced the cold caloric test (Baloh and Kerber 2011b).

2.7 LABORATORY EXAMINATION OF ANGULAR VESTIBULO-OCULAR REFLEXES

2.7.1 MEASUREMENT OF EYE MOVEMENTS

Measurement of eye movements is essential to the objective evaluation of the VOR. Current methods include electro-oculography (EOG), magnetic search coil, and VOG.

2.7.1.1 Electro-oculography

EOG is the simplest system for recording eye movements, and has been most widely used. Two electrodes, placed horizontally and vertically on each eye, sense the changes in the electric dipole between the retina and cornea when the eye is moving (Brandt and Strupp 2005). EOG is easily administered, noninvasive, relatively inexpensive, and does not interfere with vision (Baloh and Kerber 2011b). EOG is fairly accurate in detecting horizontal eye movements at ±40° with an accuracy of approximately 1° and vertical movements of ±20°. Recording the vertical eye movements is, however, susceptible to artefacts especially those that derive from eyelid movements. EOG cannot measure torsional eye movements and has a poor signal-to-noise ratio. It is also dependent on lighting conditions because the electric dipole changes with the amount of light striking the retina, which necessitates repeated calibration (Brandt and Strupp 2005, Hullar et al. 2005, Baloh and Kerber 2011b).

2.7.1.2 Magnetic search coil

The magnetic search coil method uses a contact lens that contains coils. These coils are able to sense eye movements in an oscillating magnetic field in three planes (horizontal, vertical, and torsional) to a high accuracy of about 0.02°, even during rapid head movements (Hullar et al. 2005, Prepageran et al. 2005). It has also been the gold standard for scientific eye movement recording as it has low noise. It is an invasive method and therefore the recording time for the method is limited to about 30 minutes (Brandt and Strupp 2005, Houben et al. 2006). Another drawback is that the method is technically demanding to carry out. Thus, the magnetic search coil method is generally limited to scientific use (Brandt and Strupp 2005, Baloh and Kerber 2011b).

2.7.1.3 Video-oculography

VOG is replacing EOG in clinical laboratories (Baloh and Kerber 2011b). Two-dimensional VOG equipment is capable of recording horizontal and

vertical eye movements. Modern three-dimensional VOG (3D-VOG) system, with infrared video cameras integrated into the VOG mask that monitors the pupil and the iritic pattern, allows measurement of eye movements in three dimensions like that of the magnetic search coil method, except it is non-invasive (Hirvonen and Aalto 2009). Sampling rate of 50-60 Hz has somewhat limited the recording quality of the VOG, especially for detecting saccades, but modern VOG versions have sufficient temporal and spatial resolution even compared to magnetic search coil method (Houben et al. 2006). The resolution for the VOG is largely linear in eye movements of ± 30° (Brandt and Strupp 2005). Muscle artefacts do not affect VOG recording, but recording is only possible when the eyes are open, and eye blinks interfere with VOG recording. Problems with the digital tracking system may occur when patients have poor contrast between the pupil and iris (Baloh and Kerber 2011b).

An integrated head position sensor with the VOG mask allows a direct evaluation of the head position. Lightweight VOG goggles that are designed for minimal slippage to allow accurate recording of eye movements during HIT have been developed recently, and are commercially available (video HIT) (Bartl et al. 2009, MacDougall et al. 2009, Newman-Toker et al. 2013). The video HIT has a sampling rate of > 200 Hz, and it reliably recognizes even dysfunction of the vertical SCCs (Macdougall et al. 2013).

2.7.2 CALORIC TEST

The bithermal caloric test still has a central role in examination of a dizzy patient. It allows testing both labyrinths independently: cool and warm stimulus (water or air) applied to the ear canal either excites or inhibits the labyrinth, and the concomitant nystagmus is recorded. The caloric response features a considerable interindividual variability that depends on, inter alia, the individual temporal bone anatomy (Davidson 1988), thus the absolute values of the slow-phase nystagmus often have little value. The level of significant asymmetry in the caloric response (the peak slow-phase velocity of nystagmus) between the right and left labyrinth indicates a unilateral deficit of the VOR and varies between laboratories, but generally an asymmetry of 20—30% is considered pathological (Aw et al. 2001, Prepageran et al. 2005, Brandt and Strupp 2005, Hullar et al. 2005, Wuyts et al. 2007, Baloh and Kerber 2011b, Bartolomeo et al. 2013). Murnane et al. (2009) suggested that monothermal (warm) water irrigations often offer adequate diagnostic value.

The horizontal SCC lies closest to the external auditory canal, thus the caloric response is mainly produced by the horizontal SCC, and caloric stimulation of the vertical canals is unreliable (Wuyts et al. 2007). The major limitation of the caloric test is that it generates only a non-physiological stimulation of

the labyrinth, with a frequency of 0.003 Hz (Fife et al 2000). This is well below normal frequencies of the head of 1 to 8 Hz and well below the ideal operating range of the aVOR (Hess et al. 1985, Prepageran et al. 2005).

2.7.3 ROTATIONAL TESTS WITH SINUSOIDAL HEAD OSCILLATIONS

Sinusoidal rotational tests that use whole-body or head-on-body rotation, allow testing of multiple frequencies of more physiological stimuli than detected by the caloric test, and do not involve the physical features of the temporal bone (Fife et al. 2000). Sinusoidal rotational tests, however, affect both labyrinths simultaneously, and are therefore less practical at detecting unilateral vestibular deficits (Brandt and Strupp 2005).

2.7.3.1 Rotational chair test: sinusoidal stimulation

A commercially available motor-generated chair provides passive whole-body yaw plane oscillations in different stimulus profiles. The test is performed in total darkness to avoid fixation of the eyes, and the patient should also perform continuous mental tasks to maintain alertness. The eye movements are measured and compared to the input stimulus to quantify the VOR gain, phase, and asymmetry, which can be measured in multiple frequencies that range from about 0.01 Hz to 1.0 Hz (Wuyts et al. 2007). The test is useful in assessing patients with bilateral vestibular deficit (Hullar et al. 2005). The stimulation frequency and acceleration, however, are too low for detecting or monitoring unilateral vestibular lesions (Halmagyi et al. 2001). Other limitations of the rotational chair test include the expense of the equipment, and the dependence of the measures on the mental alertness of the patient (Fife et al. 2000, Wuyts et al. 2007). Sinusoidal whole-body rotations with higher frequencies and velocities (up to 11 Hz and 120°/s) have also been used, but with little additional diagnostic value compared to caloric test, bedside HIT, or quantitative HIT (Kessler et al. 2008). Head slippage was also reported to be a problem with high-frequency rotational chair testing (Hydén et al. 1984).

2.7.3.2 Head autorotation test

In the head autorotation test, the patient is usually asked to rotate his/her head in the yaw axis, in a sinusoidal pattern that is typically within the range of 0.5 to 6 Hz (O'Leary and Davis 1990, Hirvonen et al. 1997, Blatt et al. 2008). During the active head movement the patient's gaze fixates on a target, and the eye movements are recorded usually by EOG. Gain and phase can be defined by comparing the eye and head velocities. The advantage of the head autorotation test is that it operates within the natural frequency range of the VOR. The asymmetry in the head autorotation test response has

been found to correlate with the side of the lesion in patients with VS or unilateral labyrinthectomy (O'Leary et al. 1991), but in other studies the test has been found to be poor at detecting unilateral vestibular loss (Fife et al. 2000, Della Santina et al. 2002). Nonvestibular eye movement systems, such as preprogrammed eye movements, can contribute to the response and enhance the response compared to passive head impulse testing (Hirvonen et al. 2000, Della Santina et al. 2002, Halmagyi et al. 2003). Responses may also vary with practise, and patients may have difficulty performing the head movements (Blatt et al. 2008).

2.7.4 ROTATIONAL TESTS WITH IMPULSIVE HEAD MOVEMENTS

2.7.4.1 Rotational chair test: stepwise stimulation

The rotational chair can also be used to provide impulsive head-on-body rotations, when the chair accelerates in darkness to peak velocities of between 60 to 240°/s in about 1 s, whereas the eye movements are recorded (Hullar et al. 2005). Few data on rotational chair-provided transitional stimuli exist, partly because the technical limitations of the conventional rotational chair equipment (Collewijn and Smeets 2000). A more powerful whole-body rotator has been developed with an acceleration of up to 2800°/s² and a peak velocity of 190°/s (Crane and Demer 1998). In this test setting, the patients were instructed to fixate their gaze on a target, which is the contrary to that done in conventional rotational chair testing.

2.7.4.2 Quantitative head impulse test

The quantitative HIT usually includes manually delivered passive, high-acceleration head impulses as in the bedside HIT, while quantitatively monitoring the head and eye motion. First results with the quantitative HIT were reported in patients having undergone unilateral vestibular neurectomy, in which the VOR gain was substantially asymmetric so that the gain on the ipsilateral side was severely decreased, but only mildly deficient on the contralateral side (Halmagyi et al. 1990). This on-off asymmetry of the aVOR responses cannot be detected by tests that use low-acceleration rotations, therefore such tests are unsuitable for monitoring unilateral vestibular lesions (Halmagyi et al. 2001).

The patient sits upright in a dimly lit room, and his gaze fixates on a light-emitting diode target at a distance from about 90 to 300 cm (Weber et al. 2008, Newman-Toker et al. 2013). Several rapid, unpredictable head impulses are delivered manually by the examiner who stands behind the patient and most commonly delivers the impulses along the horizontal plane,

though testing the superior and posterior SCCs is also possible (Halmagyi et al. 2001). The eye and head movements are usually monitored using the magnetic search coil technique (Clarke 2010), although data with lightweight and high frame rate VOG goggles have also been presented (Bartl et al. 2009, MacDougall et al. 2009). With the magnetic search coil method, the eye movement is measured by using a contact lens placed either on one or both eyes. The head movement is measured with a coil, which is either mounted on a bite bar, fixed to the forehead with tape, or fixed to the nosepiece of a lightweight spectacle frame (Schmid-Priscoveanu et al. 2001, Halmagyi et al. 2003, Weber et al. 2008). Only the compensatory eye movements that occur at the first 150 ms after the onset of the head movement should be analyzed to minimize the impact of the cervico-ocular reflex, visual pursuit reflex, or the saccadic system (Halmagyi et al. 2001).

The properties of the head impulse stimuli vary considerably between studies. The amplitude has varied from 10 to 40°, velocity from 80 to 400°/s, and acceleration from 800 to 10 000°/s² (Schmid-Priscoveanu et al. 2001, Lasker et al. 2002, Jorns-Häderli et al. 2007).

2.7.4.3 Reactive torque helmet

Tabak and Collewijn (1994) introduced the reactive torque helmet for measuring aVOR. A helmet that has a torque motor on top is worn by a seated subject who fixates on a target, and its motor generates unpredictable horizontal head rotations. Eye and head movements are recorded by the magnetic search coil method. The torque-driven helmet reaches velocities of about 80°/s and accelerations of about 770°/s² with amplitudes of 10—20° (Tabak et al. 1997b, Tabak et al. 1997c). The authors regarded the uniform acceleration-producing torque helmet method as superior to manually delivered impulses (Tabak and Collewijn 1994).

In normal subjects, the gain measured by the torque helmet method was near unity (Tabak and Collewijn 1994, Tabak and Collewijn 1995, Tabak et al. 1997b, Collewijn and Smeets 2000). In patients with total unilateral vestibular loss, the mean gain was 0.59 on the ipsilateral side, and 0.94 on the contralateral side (Tabak et al. 1997c).

The motorized head impulse rotator was developed in Helsinki University Central Hospital to quantify the horizontal VOR in response to uniform high-acceleration head impulses (Aalto et al. 2002). Data obtained from mHIT in heathy subjects and patients with VS have been reported before (Hirvonen et al. 2007, Hirvonen et al. 2008).

2.8 CLINICAL EXAMINATION OF OTOLITHIC FUNCTION

Signs of ocular tilt reaction that results from unilateral otolith deficiency can be discernable, most notably the skew deviation whereby the pupil on the intact side is elevated and the pupil on the lesioned side is depressed (Halmagyi et al. 1979, Ramat et al. 2001). Head tilting may be difficult to notice by inspection in humans, because graviceptive signals provide the predominant input for SVV (Tarnutzer et al. 2010).

2.8.1 HEAD HEAVE TEST

The head heave test was introduced as a bedside test for evaluating dynamic otolith-ocular responses, or the utricular function and the lVOR using a similar rationale and strategy to that of the HIT (Ramat et al. 2001). The head of the patient is moved manually to left and right in a horizontal plane with brief, brisk motions. Normal subjects are able to maintain fixation on the target by compensatory eye movements opposite to the direction of head movement, unlike those patients with unilaterally deficient utricular function, in which a corrective saccade is observed (Brandt and Strupp 2005). In patients with VN, the head heave test and HIT data correlate, although the authors stress that the response in head heave test is inherently undercompensatory in normal subjects, who exhibit typically slight corrective saccades in both directions (Mandalà et al. 2008). Thus, the asymmetry of the responses should indicate when the test is abnormal, in contrast to the HIT, in which the asymmetry in the response is usually explicit. The response to the head heave test can also be measured quantitatively, and a special head sled may be used to obtain more reproducible translational stimuli, and to minimize any unwanted head rotation (Ramat et al. 2001, Kessler et al. 2007, Mandalà et al. 2008). The variability of the lVOR gain and the insensitivity of the head heave test diminish its utility as a clinical test (Paige 2002).

2.9 LABORATORY EXAMINATION OF OTOLITHIC FUNCTION

2.9.1 MEASUREMENT OF OCULAR TORSION

The ocular torsion related to head tilting or after unilateral vestibular loss has earlier been measured by using fundus photography (Halmagyi et al. 1979, Curthoys et al. 1991b, Curthoys et al. 1991a). More recently, the fundus photography has been largely replaced by the magnetic search coil method or by 3D-VOG (Schworm et al. 2002, Zingler et al. 2006). The fundus images are obtained by having the centres of the pupils lie in an exactly horizontal line. The amount of the ocular torsion is measured by comparing

photographs taken during different visits, such as before and after vestibular neurectomy. The ocular torsion responses are too variable for reliably identifying the side of the unilateral vestibular lesion (Baloh and Kerber 2011b).

2.9.2 SUBJECTIVE VISUAL HORIZONTAL/VERTICAL TEST

As a relatively simple method with findings easy to interpret, the SVH/SVV test has commonly been used for assessing utricular function. This psychophysical test primarily reflects ocular torsion. The subject sits with his/her head upright in total darkness, thus any visual cues of the surroundings are excluded. Then, the subject adjusts a dimly illuminated bar to a perceived horizontal or vertical position (Halmagyi and Curthoys 1999). The visual surroundings can also be excluded by limiting the subject's visual field (Vibert and Häusler 2000, Zwergal et al. 2009). A normal subject is able to set the bar within 2° of the true gravitational horizontal or vertical plane (Böhmer and Rickenmann 1995, Tabak et al. 1997a). The trial-to-trial variability is minimal in the head upright position. In whole-body roll orientations, the SVV error is increased so that at body angles of < 60° it is overcompensated and at body angles of > 60° it is undercompensated. These show errors of up to 40° that peak between roll angles between 90 and 130°. The trial-to-trial variability increases with increasing roll position (Tarnutzer et al. 2010).

2.9.3 VESTIBULAR-EVOKED MYOGENIC POTENTIALS

Air and bone conducted sounds activate the otolith afferents but rarely the semicircular canal afferents, as shown in animal studies (Curthoys et al. 2006). Vestibular-evoked myogenic potential response persists despite profound sensorineural hearing loss (Baloh and Kerber 2011b). The cVEMP is produced by the inhibition of the motor neurons of the sternocleidomastoid muscle from the saccule as a primarily uncrossed inhibitory vestibulospinal response (Uchino et al. 1997, Oh et al. 2013). More recently, it was found that the VEMP can also be recorded near to the eyes (oVEMP), which reflects a crossed excitatory response of the inferior oblique eye muscle that is a form of the VOR that is primarily derived from the utricle (Todd et al. 2007, Iwasaki et al. 2009, Rosengren and Kingma 2013, Oh et al. 2013).

When recording the cVEMP, the electrodes are placed over the most prominent part of the sternocleidomastoid muscle, and the reference electrodes are placed over the clavicles. The recording is performed on a contracted muscle, which is achieved when the supine subject raises his or her head. The stimulus is usually an air or bone conducted high-intensity low-frequency sound. In contrast, when recording oVEMPs the most

consistent potentials are obtained from electrodes that are placed beneath the eyes and on the cheeks on an upward-gazing subject (Baloh and Kerber 2011b).

The oVEMP appears to correlate best with SVH/SVV and caloric responses rather than with the cVEMP, as would be expected for a test that mostly covers the superior vestibular nerve (Lin and Young 2011, Murofushi et al. 2011). The correlation between the SVH/SVV and oVEMP should, however, be expected only during the acute stage of the vestibular loss, because the SVH/SVV improves over time whereas oVEMP remains abnormal. The clearest clinical application for VEMPs is in the diagnostics of the superior semicircular canal dehiscence syndrome and other third window disorders, in which the threshold for VEMPs are characteristically low (Rosengren and Kingma 2013).

3 AIMS OF THE STUDY

The aims of the study were to evaluate the feasibility of head tilt testing and the motorized HIT for the quantification of vestibular function and its possible change in different otoneurological patient groups.

The specific aims were:

1. To assess directly possible head tilting after acute unilateral vestibular loss during the acute stage and after three months (I), and before and after VS surgery (IV).

2. To quantify the horizontal aVOR with the mHIT after acute unilateral vestibular loss, and to quantify the possible recovery of the horizontal aVOR function after three months (II).

3. To quantify the horizontal aVOR by using the mHIT in CI recipients, and to compare their pre- and postoperative horizontal aVOR function (III).

4 MATERIAL AND METHODS

All the studies in this dissertation were approved by the ethics committee of Helsinki University Central Hospital.

4.1 PATIENTS AND SUBJECTS

In Study I, head tilting was measured in 30 patients (18 female, 12 male; mean age ± standard deviation (SD) 48 ± 16, range 14—71 years) with acute unilateral vestibular loss, of which 15 returned for the follow-up measurement at mean of three (range 2—9) months later. Twenty healthy subjects (12 female, 8 male; mean age 43 ± 12, range 27—62 years) with no otoneurological diseases or medications were recruited from the hospital personnel as controls.

In Study II, the aVOR was measured in 30 patients (16 female, 14 male; mean age 47 ± 16, range 14—71 years) with acute unilateral vestibular loss. Twenty (67%) patients returned for the follow-up measurement on average three (range 1—9) months later.

In Study III, 44 CI recipients (28 female, 16 male; mean age 55 ± 13, range 30—76 years) were measured with the mHIT preoperatively. Forty-one patients returned for postoperative measurement at two (range 1—5) months (early follow-up visit), and 27 patients at 19 (range 11—50) months (late follow-up visit) after CI surgery. A total of 24 patients were tested three consecutive times.

In Study IV, head tilting was measured consecutively in 43 patients with an unilateral VS (22 male, 21 female; mean age 55 ± 11, range 28—72 years) preoperatively, and four (range 3—6) months postoperatively. The same group of healthy subjects as in Study I served as controls.

4.2 METHODS

4.2.1 EQUIPMENT AND MEASUREMENT

4.2.1.1 Head tilt testing (Studies I and IV)

Head tilting was measured by using a commercially available VOG mask-integrated head position sensor (3D VOG Video-Oculography, Version 5,

Sensomotoric Instruments, Berlin, Germany) (Figure 3). The VOG mask was firmly attached to the head by an elastic strap, and any significant slippage of the mask was excluded by monitoring the eye position in the centre of each eye screen.

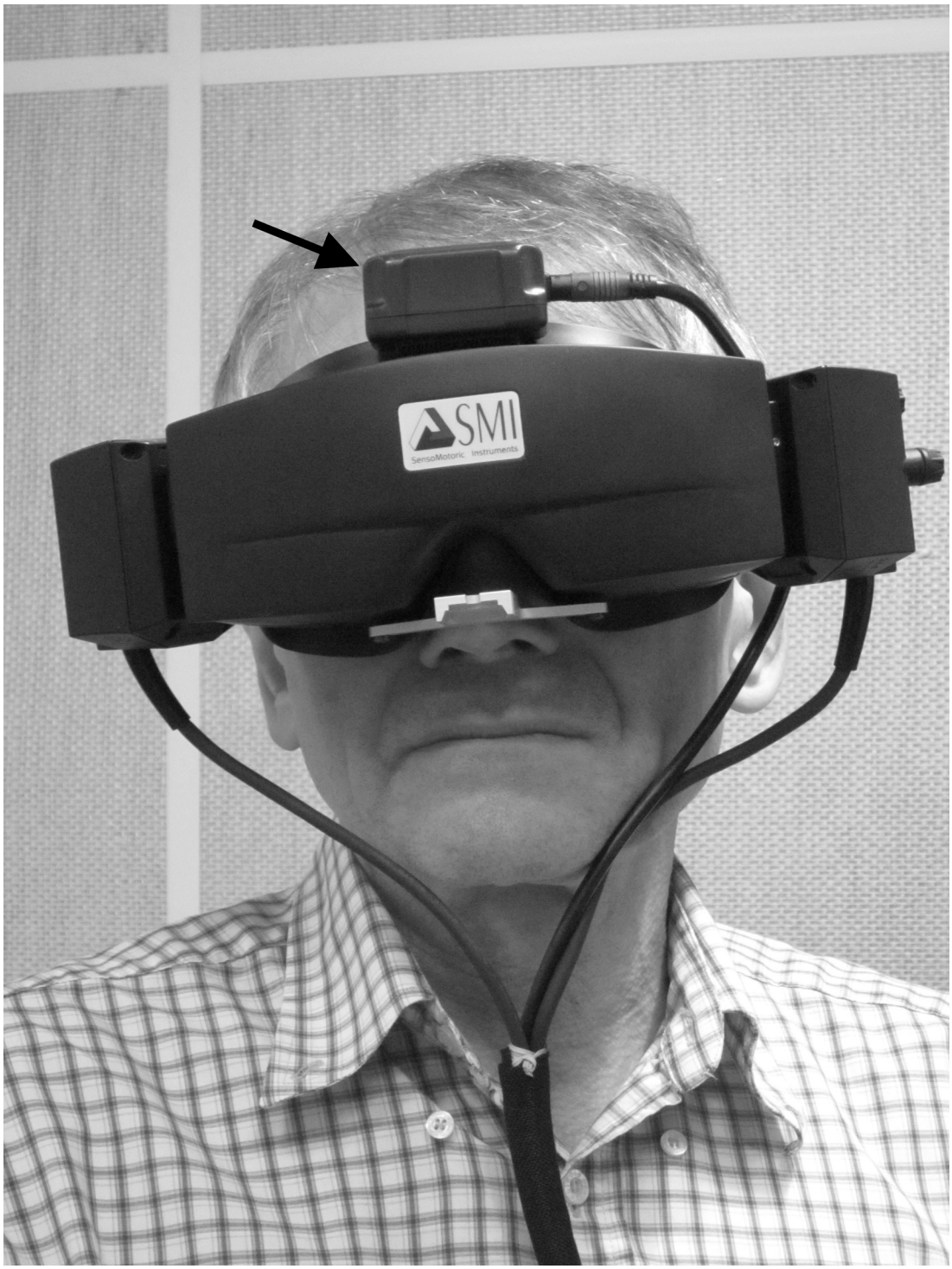

Figure 4 A subject wearing the VOG mask showing the integrated head-position sensor on top of the mask (arrow).

The recording of the head position was performed in the same order for each patient. The patients were seated head upright and eyes uncovered in a dimly lit room, and they were asked to keep the head as straight as possible. This position was used as the reference position of the head. Next, the patients' eyes were covered with the VOG mask cover to achieve total darkness, and then they were instructed to maintain their head position. The angles of the possible tilting of the head was monitored during the following 30 s (static head tilt).

The dynamic part of the measurement involved three lateral tilts of the head of about 30—40° towards each shoulder (roll plane) in total darkness. The patients kept their head tilted for approximately 15 s, after which they were instructed to return their heads to the assumed upright position for approximately 15 s. The angles of the possible tilting of the heads compared to the reference positions were measured at the end of each position. The mean deviation from the reference position of the three returns was calculated separately for both sides, and as a mean for both sides (subjective head vertical, SHV).

4.2.1.2 Motorized head impulse test (Studies II and III)

The horizontal aVOR was measured by the motorized head impulse rotator. A motor and gear combination (DC motor GR 63 x 25 and planetary gear PLG 52.0; Dunkermotoren Alcatel SEL AG, Bonndorf, Germany) generated passive, unpredictable horizontal head-on-body rotations. The motor and gear were fixed to a rigid chair backrest, with the rotating plate attached to an upwards-lying axle. The rotator delivered the head impulses to a tightly fastened leather helmet via two pushrods from the rotating plate on both sides. Plastic straps from an industrial worker's safety helmet allowed individual fitting and fastening of the helmet in the horizontal and oblique planes. For safety, the maximum turning angle of the rotating plate was mechanically limited to ± 30°. A rotating joint attached to a support bar stabilized the top of the helmet by eliminating anteroposterior head movement. Lateral movement was reduced by two stabilizing rods attached to the bar and the chair.

The motor was driven by a pulse of increasing voltage fed to the motor driver (LA-5600, linear drive amplifier, Electro-Craft Corporation, Motor & Control System Division of Robbins & Myers, Minneapolis, MN, USA) to obtain the short torque impulse (Aalto et al. 2002). A constant acceleration of approximately 2000°/s² during the first 120 ms was produced for each impulse to determine the proper pulse waveform. A reversal of the driving voltage to the motor enabled the active braking. Driving the motor at a slower pace returned the helmet to the starting position.

The head position was monitored by a rotation-angle sensor (type CP-2UT; Midori Precisions Co., Ltd, Tokyo, Japan), which was directly attached to the helmet. The sensor had a noise velocity of less than 0.1°/s. No significant decoupling of the helmet and the head has been observed with the used stimulus profile. A conventional EOG was applied to monitor the eye position: two active electrodes were attached to the lateral canthi of the eyes without coupling to the helmet, and the earth electrode was fixed to the forehead. The EOG signal was amplified and low-pass filtered with a 30 Hz cut-off frequency before the analog-to-digital conversion. A sampling frequency of 400 Hz and a resolution of 16 bit were used for recording the eye and head movement signals. The EOG signal was further low-pass filtered with a cut-off frequency of 10 Hz before analysing it. The EOG signals had a noise velocity less than 5°/s. Calibration of the eye movement was performed before each test by recording horizontal saccades of ± 10°.

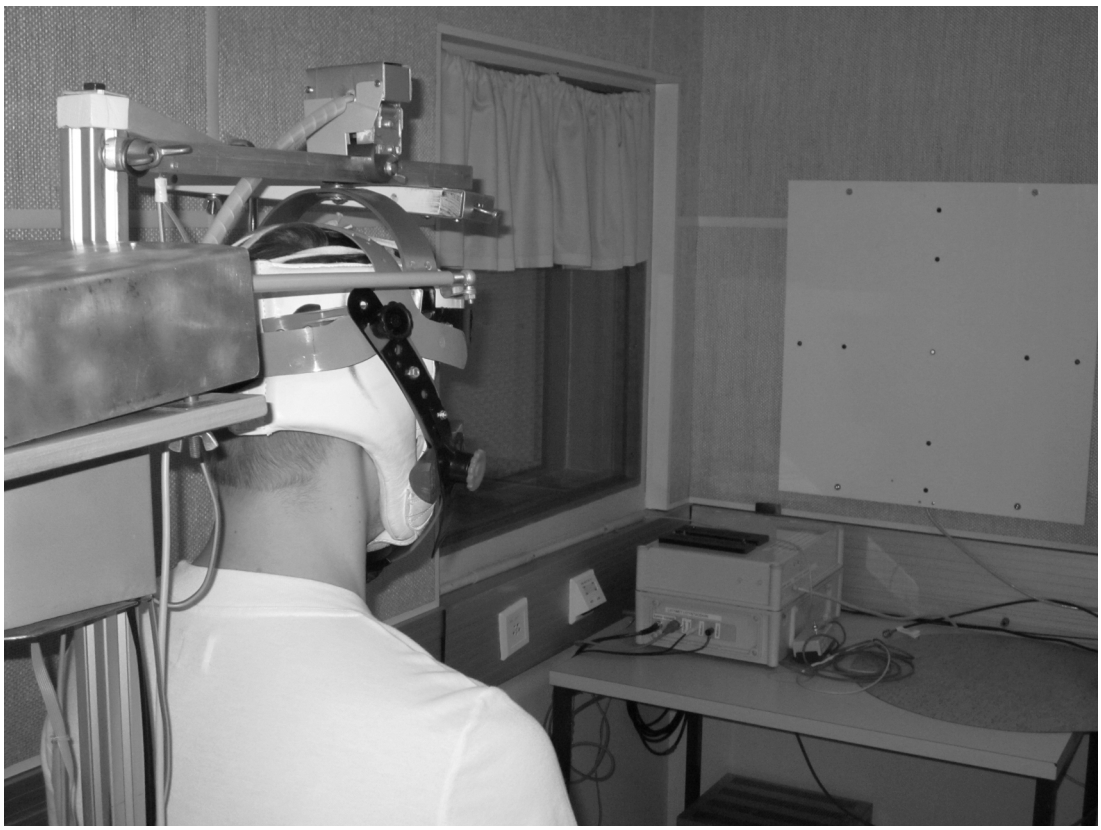

Figure 5 The motorized head impulse rotator. The subject wears a tightly fastened helmet and fixates on a light-emitting diode target at a distance of 140 cm. Electro-oculography is used for recording the eye movements, and the head position is recorded with a rotation-angle sensor.

The patient wears the tightly fastened but comfortable helmet sitting upright then instructed to fixate at a light-emitting diode target at a distance of 140 cm, on the midline, and at the eye level (Figure 5). The head-on-body rotations delivered by the motorized head impulse rotator were randomized

for direction and time interval between the individual rotations (range 1.0-1.4 seconds). The head impulses had a mean ± SD acceleration of 1550 ± 240°/s², peak head velocity of 170 ± 27°/s, and amplitude of 21 ± 3° in normal subjects, (Hirvonen et al. 2007). The mean acceleration was 2050 ± 260°/s², and the peak head velocity was 168 ± 20°/s in VN patients. The mean duration of the head impulse from the beginning of the head motion to the peak head velocity was 120 ms. Each test consisted of about 23—30 impulses towards each side (left and right).

4.2.2 ANALYSES

4.2.2.1 Head tilt testing (Studies I and IV)

The head tilt testing comprised four different parameters: static head tilt, mean SHV, ipsilateral SHV, and contralateral SHV. The static head tilt and the mean SHV were not direction sensitive to allow better comparison to the normative data. In the ipsi- and contralateral SHV, the positive sign indicated tilting towards the ipsilateral side, and negative sign indicated tilting towards the contralateral side. Head tilting of < 2° was considered normal, 2 < 3° moderately abnormal, and ≥ 3° definitely abnormal, according to the data on healthy subjects (Studies I and IV).

4.2.2.2 Motorized head impulse test (Studies II and III)

The processed eye and head movement signals were entered into data analysis software (Eye Movement Analyzer, version 37; Migliaccio, A.), which was run on the Labview program, version 7.1 (National Instruments, Austin, TX, USA). Any data with prominent noise or artefacts commencing before the onset of the head movement were discarded manually from the analysis. Impulses with head velocities less than 100°/s and with eye velocities higher than 20°/s at the beginning of the head movement were also excluded. The onset of the head movement was determined as the time when the head velocity reached 10°/s.

The horizontal aVOR gain was calculated as the ratio of the eye and head velocities during the 30 ms period before the peak head velocity. The gain values for the testing distance of 140 cm were normalized to infinity (Mansson and Vesterhauge 1987). The asymmetry in gain between right and left rotations was calculated by the following equation: ([gain right – gain left] / [gain right + gain left]) x 100%. Gains of < 0.84 and asymmetry of > 10% was considered pathological according to the data on healthy subjects (Hirvonen et al. 2007).

4.2.3 SUBJECTIVE SENSATION

In all the studies, the patients completed a structured questionnaire during their visits to the vestibular laboratory (see Appendix). They assessed their hearing, the frequency and intensity of dizziness, its effect on their quality of life, and their general quality of life, on a scale from 1 to 5, in which the larger number indicated more severe symptoms.

4.2.4 STATISTICS

IBM SPSS, version 19 software (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. P-values below 0.05 were considered to be statistically significant.

In Study I, the non-paired t-test was used to compare the groups, and the correlations between the vestibular test signs and symptoms were calculated for the Spearman correlation test. In Studies II and III, the non-paired t-test and one-way analysis of variance were applied for comparison of groups, and the Pearson's correlation test was used to determine the correlations between signs and symptoms. In Study IV, the non-paired t-test was applied to compare the patients and controls, and the paired t-test for consecutive comparisons in patients, and the Pearson's correlation test for correlations between signs and symptoms.

5 RESULTS

5.1 HEAD TILT TESTING (STUDIES I AND IV)

5.1.1 HEALTHY SUBJECTS

The mean ± 95% confidence interval static head tilt for the control group was 1.0 ± 0.4°. The mean SHV was 1.2 ± 0.5°.

5.1.2 PATIENTS WITH ACUTE UNILATERAL VESTIBULAR LOSS (I)

The mean ± 95% confidence interval static and dynamic head tilt in the patients with acute unilateral vestibular loss are illustrated in Table 1.

Table 1 *Mean ± 95% confidence interval static head tilt, subjective head vertical (SHV), and SHV when the head is returning from ipsi- or contralateral side in patients with acute unilateral vestibular loss measured in the acute stage and on average 3 months later, and static head tilt and SHV in control subjects. Static head tilt and mean SHV result from the absolute values of the individual tilts. In side-specific SHV the positive sign indicates tilting towards the ipsilateral side, and the negative sign indicates tilting towards the contralateral side.*

	Controls n = 20	Acute n = 30	Follow-up n = 15
Static head tilt (°)	1.0 ± 0.4	2.6 ± 1.1	1.1 ± 0.5
Mean SHV (°)	1.2 ± 0.5	3.4 ± 0.7	1.7 ± 0.7
Ipsilateral SHV (°)		4.9 ± 1.0	1.4 ± 1.6
Contralateral SHV (°)		2.0 ± 1.0	–1.5 ± 1.5

The static head tilt in patients in the acute stage was statistically significantly greater than during their follow-up visit ($p = 0.008$), or compared to healthy controls ($p = 0.004$). During the follow-up, no significant difference in the static head tilt existed between the patients and healthy controls ($p = 0.70$). The static head tilt in the acute stage was definitely abnormal in 37%, moderately abnormal in 23%, and normal in 40% of the patients. In those patients with abnormal static head tilt, all but one (5%) tilted towards the ipsilateral side. During the follow-up visit, the static head tilt was definitely abnormal in 7%, moderately abnormal in 20%, and normal in 73% of the patients. Of the four patients with an abnormal tilt, three tilted towards the ipsilateral side.

The mean SHV in patients at the acute stage was significantly greater than during the follow-up visit ($p < 0.001$), and compared to controls ($p < 0.001$). During the follow-up testing, no significant difference ($p = 0.232$) of the

mean SHV was detected between the patients and controls. The mean SHV during the acute stage was definitely abnormal in 60%, moderately abnormal in 20%, and normal in 20% of the patients. No patients showed a mean SHV towards the contralateral side in the acute stage. During the follow-up, the mean SHV was definitely abnormal in 20%, moderately abnormal in 20%, and normal in 60% of the patients. Of the patients with abnormal tilt, 50% tilted towards the contralateral side.

During the acute stage, when both sides were evaluated separately, the ipsilateral SHV was incomplete, and the head also tilted towards the ipsilateral side after returning from the contralateral side. During the follow-up visit the contralateral SHV changed so that it was slightly tilted towards the contralateral side. In the acute stage, 80% of the patients manifested greater SHV when returning the head from the ipsilateral side.

Head tilt correlated with the asymmetry in the horizontal VOR gain ($r = 0.87$, $p < 0.001$), and the slow-phase velocity of spontaneous nystagmus ($r = 0.85$, $p < 0.001$). The score for the intensity of dizziness decreased significantly from 3.1 ± 0.4 to 1.4 ± 0.4 during the follow-up ($p < 0.001$). The dizziness-related quality of life scores improved from 3.8 ± 0.6 to 1.7 ± 0.5 ($p < 0.001$). The symptoms had no association with the head tilt.

5.1.3 PATIENTS WITH VESTIBULAR SCHWANNOMA (IV)

The mean ± SD static and dynamic head tilt in the patients with VS are illustrated in Table 2.

Table 2 *Mean ± SD static head tilt, mean subjective head vertical (SHV), and SHV when the head is returning from ipsi- or contralateral side, in patients with vestibular schwannoma measured preoperatively and a mean of four months postoperatively, and static head tilt and SHV in control subjects.*

	Controls n = 20	Preoperative n = 43	Postoperative n = 43
Static head tilt (°)	1.0 ± 0.9	1.6 ± 1.5	1.7 ± 1.5
Mean SHV (°)	1.2 ± 1.0	2.0 ± 1.9	2.5 ± 1.8
Ipsilateral SHV (°)		2.8 ± 3.3	3.3 ± 3.0
Contralateral SHV (°)		-0.5 ± 3.0	0.6 ± 3.2

The static head tilt in patients was significantly greater than in controls both preoperatively ($p = 0.043$), and postoperatively ($p = 0.011$). No change occurred between the pre- and postoperative static head tilt ($p = 0.62$). The static head tilt was preoperatively definitely abnormal in 21%, moderately abnormal in 21%, and normal in 58% of the patients. Of the patients with abnormal static head tilt, 83% tilted towards the ipsilateral side, and 17% towards the contralateral side. The static head tilt postoperatively was

definitely abnormal in 25%, moderately abnormal in 19%, and normal in 56% of the patients. Of the patients with abnormal static head tilt, 84% tilted towards the ipsilateral side, and 16% towards the contralateral side. The tumour size correlated with the preoperative static head tilt ($r = 0.45$, $p = 0.005$).

Both preoperative ($p = 0.027$) and postoperative ($p = 0.001$) mean SHV in patients were significantly greater than in control subjects. The mean SHV increased non-significantly after surgery ($p = 0.304$). The preoperative mean SHV was definitely abnormal in 23%, moderately abnormal in 14%, and normal in 63% of the patients. Of the patients with abnormal SHV, 75% tilted towards the ipsilateral side, and 25% towards the contralateral side. The mean SHV postoperatively was definitely abnormal in 37%, moderately abnormal in 21%, and normal in 42% of the patients. Of the patients with abnormal SHV, 92% tilted towards the ipsilateral side, and 8% towards the contralateral side.

When evaluated separately, the ipsilateral SHV was significantly greater than the contralateral SHV both preoperatively ($p = 0.001$) and postoperatively ($p < 0.001$). The ipsilateral SHV increased non-significantly after surgery ($p = 0.46$). The contralateral SHV changed direction and deviated towards the contralateral side in the preoperative testing, but towards the ipsilateral side in the postoperative testing. This change was non-significant, however ($p = 0.12$).

The mean preoperative word recognition was 75 ± 30% (range 0-100%) ipsilaterally, and 97 ± 4% contralaterally. The ipsilateral ear had residual hearing (pure tone average 26—78 decibels, word recognition 48—96%) in 21% of the patients postoperatively.

The intensity of dizziness increased significantly after surgery ($p = 0.040$), but the frequency of dizziness ($p = 0.053$) and its effect on the quality of life ($p = 0.158$) did not change significantly. Dizziness had at the most mild (symptom scores 1 or 2) effect on quality of life in the majority of patients both before (79%) and after surgery (67%).

5.2 MOTORIZED HEAD IMPULSE TEST (STUDIES II AND III)

5.2.1 PATIENTS WITH ACUTE UNILATERAL VESTIBULAR LOSS (II)

The mean ± SD aVOR gain and asymmetry are presented in Table 3. Both early ($p < 0.001$) and late ($p = 0.014$) ipsilateral gain were significantly lower

than the respective contralateral gain. The asymmetry ($p < 0.001$) and the ipsilateral gain ($p < 0.001$) improved highly significantly during the follow-up period of some months. The contralateral gain improved non-significantly ($p = 0.36$). An example of the gain recovery after an initial loss of unilateral vestibular function is illustrated in Figure 4.

Table 3 *The mean ± SD high-acceleration horizontal aVOR gain and gain asymmetry in patients with acute unilateral vestibular loss, measured in the acute stage and a mean of three months later.*

	Acute n = 30	**Follow-up n = 20**
Ipsilateral gain	0.49 ± 0.21	0.79 ± 0.23
Contralateral gain	0.89 ± 0.14	0.94 ± 0.16
Asymmetry (%)	32 ± 18	12 ± 14

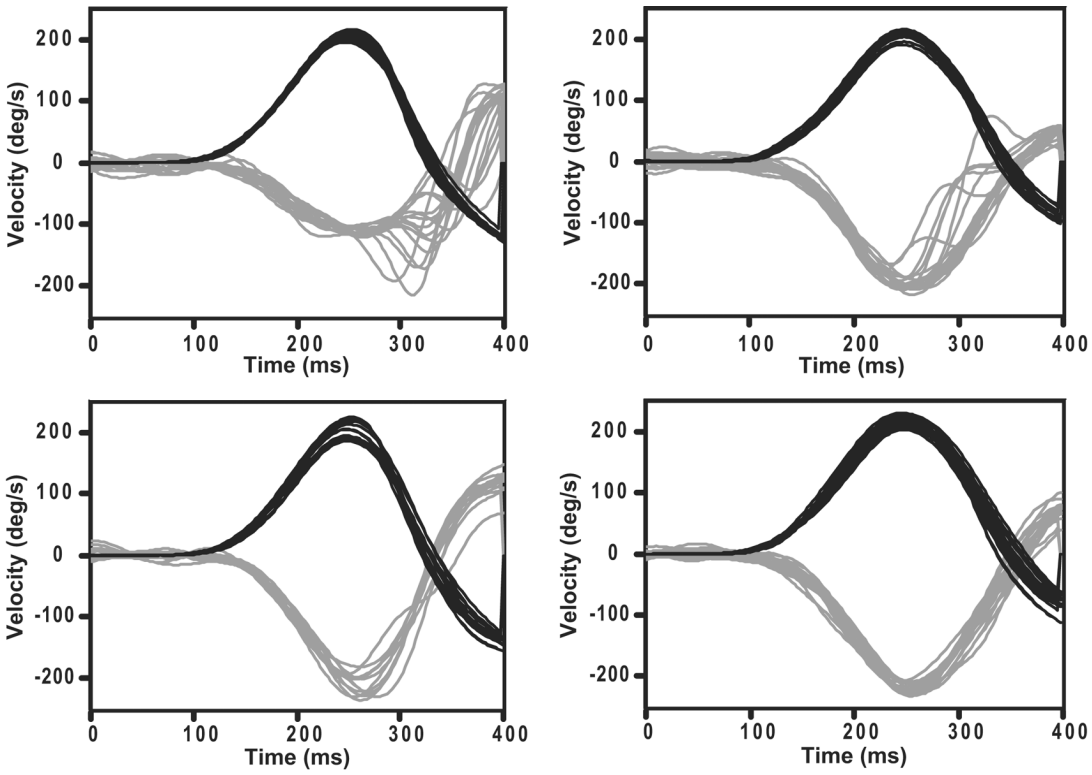

Figure 6 Motorized head impulse test recordings for a patient with VN at two days after the onset of symptoms (upper panels), and after one month (lower panels). The ipsilateral response is illustrated in the left panels, and the contralateral responses in the right panel. The black lines represent the head velocity and the gray lines the eye velocity of individual impulses over time. At the acute stage, the ipsilateral aVOR gain is decreased to 0.54 while the contralateral gain of 0.96 is normal. After one month the ipsilateral gain has recovered fully to 1.00.

The gain or asymmetry recovered fully in 45% and partially in 35% of the patients. In four patients (13%) the early asymmetry was normal, and in two

of them the ipsilateral gain was also normal, despite 3D-VOG showing spontaneous nystagmus that suggests a unilateral peripheral vestibular loss.

The intensity and frequency of dizziness improved significantly from 3.5 ± 1.0 to 1.6 ± 0.7 ($p < 0.001$). The high late symptom score significantly correlated with low late ipsilateral gain ($r = 0.47$, $p = 0.043$) and high asymmetry ($r = 0.53$, $p = 0.018$).

5.2.2 PATIENTS WITH COCHLEAR IMPLANT (III)

The mean ± SD aVOR gain and asymmetry are presented in Table 4. The ipsilateral gain showed no change between the test occasions. Moreover, the contralateral gain and asymmetry remained unchanged. The differences between the ipsilateral and contralateral gain were non-significant on all testing occasions.

Table 4 *The mean ± SD preoperative, and early (2 months) and late (19 months) postoperative high-acceleration horizontal aVOR gain and gain asymmetry in cochlear implant patients.*

	Preoperative n = 44	**Early postoperative n = 41**	**Late postoperative n = 27**
Ipsilateral gain	0.77 ± 0.26	0.75 ± 0.30	0.73 ± 0.33
Contralateral gain	0.79 ± 0.30	0.75 ± 0.31	0.74 ± 0.32
Asymmetry (%)	9 ± 11	10 ± 13	9 ± 14

The preoperative horizontal aVOR gain was impaired (< 0.84) bilaterally in 41% of the patients, while unilateral impairment was found in 11% ipsilaterally and in 5% contralaterally. In four individual patients the postoperative ipsilateral gain was evidently decreased in the early postoperative visit. Three of these had, however, already decreased gain preoperatively. Only one of these patients was measured again in the late postoperative visit and he showed no recovery in the gain. In addition, one patient had decreased gain in the late postoperative testing, and that patient's early postoperative gain had been normal. Thus, 7% of the patients had decreased ipsilateral gain after a postoperative mean of 19 months.

The frequency and intensity of dizziness, or its effect on the quality of life remained unchanged on all visits. None of the patients expressed a major increase in the dizziness scores during the follow-up, and the scores had no correlation with ipsi- or contralateral gain on any of the visits. The preoperative general quality of life score of 3.5 ± 1.2 improved significantly to 2.6 ± 1.1 in the late follow-up visit ($p = 0.01$). Low preoperative aided bilateral word recognition correlated to low ipsilateral ($r = 0.57$, $p < 0.001$) and contralateral ($r = 0.47$, $p = 0.002$) gain.

6 DISCUSSION

Static and dynamic head tilt was measured in healthy subjects and also in patients with acute unilateral vestibular loss (VN) or VS. Horizontal aVOR was measured in patients who received CI and in patients with acute unilateral vestibular loss with the motorized head impulse rotator.

The extent of head tilt in VN and VS patients can be assessed by using commercial 3D-VOG equipment with an integrated head-position sensor. In both patient groups the head tilted slightly towards the lesion side when the visual input was blocked, and the tilting was most evident after the head was returning to the centre from an ipsilateral head tilt. In the acute stage of VN and at the postoperative testing of VS patients, their heads tilted towards the ipsilateral side even when returning from the contralateral side. Head tilt of VN patients recovered significantly during the follow-up, but no significant differences between pre- and postoperative results were found in VS patients. Most patients with VN had abnormal head tilt during the acute stage, but after some months the head tilt became normalized in most patients. The numbers of patients with abnormal head tilt somewhat increased after surgery. Patients with a more severe loss of the horizontal SCC function had more prominent head tilt.

The mHIT proved to be a reliable and accurate method for measuring the horizontal aVOR in patients with either VN or CI. The mHIT showed that the aVOR gain and asymmetry were significantly decreased during the acute stage of VN, and subsequently recovered totally or partially in the majority of the patients. In 13% of the VN patients, however, the mHIT also showed normal aVOR function during the acute stage. No significant change in the mean horizontal aVOR gain or asymmetry was found with the mHIT after cochlear implantation. The horizontal aVOR function was already decreased preoperatively in about half of the CI patients. A decrease in gain was found in 10% of the individual postoperative CI patients. Thus, a worsening of the horizontal aVOR function in the high-frequency range appears to be a possible but rare complication after cochlear implantation. The mHIT provides additional information on the severity and recovery of the vestibular loss in VN patients.

6.1 HEAD TILT TESTING

6.1.1 METHODOLOGICAL ASPECTS

The equipment used in our studies was a commercial 3D-VOG device, which included an integrated head-position sensor on top of the mask. Care was taken to avoid any slippage of the mask. During the head tilt testing no rapid head movements are needed, which decreases the risk for mask slippage. The eye position was also monitored in the centre of each eye screen with VOG to exclude any significant movement of the mask relative to the head.

The advantage of measuring the head tilt by our method is that it directly measures the head tilt as a part of the ocular tilt reaction, compared to the SVH/SVV, which is a common method for testing ocular tilt reaction. The SVH/SVV indirectly measures the tilt of the visual surroundings, which primarily reflects ocular torsion (Curthoys et al. 1991b, Böhmer and Ricknenmann 1995). In addition, our method for measuring head tilt is simple, straightforward, inexpensive, accessible, and requires no complex equipment. Moreover, 3D-VOG has become standard equipment in vestibular laboratories. Thus, the evaluation of the head tilt can be easily added to a standard VOG test pattern.

As is generally the case with otolithic function testing, the problem for head tilt testing is that the responses and changes in them are minor, which mitigates against their usage as a distinctive diagnostic test. However, the head tilting in both VN and VS patients was larger than in healthy controls and deviated towards the ipsilateral side. The tilt in VN patients also correlated with the horizontal aVOR function measured by the mHIT in VN patients. These findings suggest that the method for testing head tilt seems valid and feasible for assessing the asymmetry in otolithic function, at least in these patient groups.

6.1.2 PATIENTS WITH ACUTE UNILATERAL VESTIBULAR LOSS

Prominent head tilt after unilateral vestibular lesion is a common finding in rodents (Hirvonen et al. 2005). In humans, the head-based graviceptive signals provide the predominant input for subjective visual. This explains the difficulty of noticing the head tilt by inspection only in patients even after a total unilateral vestibular loss (Tarnutzer et al. 2010).

Bergenius et al. (1996) studied SVH in patients with unilateral vestibular loss tilted in a chair at different angles, and found that they corrected the tilt angle incompletely to a greater extent when tilted towards the ipsilateral side. This directional asymmetry in tilt responses was also found in our study as the SHV deviated more when returning the head position from the

ipsilateral side, which indicates that the gravity sensation predominantly occurs in the utricle on the tilted side. During head tilt, the hair cells on one side of the utricular striola excite, and hair cells on the other side inhibit, and the directional asymmetry is due to uneven distribution of the hair cells on each side of the striola. The weaker input of the utricle in the ipsilateral side causes the utricle on the contralateral side to drive the eyes and head towards the ipsilateral side.

6.1.3 PATIENTS WITH VESTIBULAR SCHWANNOMA

The severity of balance dysfunction varies considerably between patients with VS (Saman et al. 2009). VS is usually slow-growing, thus the VS patients may have a long-term background of unilateral vestibular impairment, which has been more or less compensated at the time of the diagnosis and treatment. Today, VS may be often diagnosed at a relatively early stage, when the central compensation may still be incomplete or even before the vestibular function is affected (Maurer et al. 2002). Patients with preoperatively decreased caloric responses seem to be less dizzy postoperatively than patients with preoperatively normal responses. This suggests that patients who already have preoperative vestibular deficit compensated for respond faster to the vestibular deafferentation (Saman et al. 2009, Uehara et al. 2011). In our study, the vestibular compensation may have occurred preoperatively, but will almost certainly do so during the postoperative follow-up of a few months. Static postural and oculomotor signs compensate relatively rapidly and more completely compared to the dynamic signs, which compensate much less completely, more variably, and over a longer period of time (Darlington and Smith 2000, Hafström et al. 2004). The dynamic head tilt found in our study seemed to increase more than static tilt after surgery, although the increase was still non-significant.

In selective vestibular neurectomy, spared residual fibres facilitate and speed up of vestibular compensation (Böhmer and Rickenmann 1995, Maurer et al. 2002). In VS surgery the neural deafferentation may not be complete and residual fibres may remain. Data on the degree of neural damage are unavailable in our study. In patients with acute unilateral vestibular deficit, the recovery was reported to be due to peripheral mechanisms and to central compensation (Allum and Ledin 1999, Baloh 2003), whereas in postoperative VS patients the recovery is probably mostly due to central compensation due to permanent deafferentation. Peripheral mechanisms may, however, affect the recovery, which probably depends on the amount of the remaining residual fibres. In our studies on head tilt, the VS patients manifested greater head tilt at about four months postoperatively than for patients with acute unilateral vestibular deficit at their follow-up visit at three months after the onset of their disease. Comparison between these

patient groups is difficult since it is unknown whether the recovery was still ongoing when the follow-up measurements were being taken.

6.1.4 GENERAL ASPECTS

Head tilting seems to be comparable with the SVH/SVV in patients with acute unilateral vestibular loss, and in patients with VS. The deviation in the SVH/SVV in the acute stage of unilateral vestibular loss has varied from 2 to 10°, but the recovery in most patients has been rapid (Tabak et al. 1997a, Min et al. 2007, Choi et al. 2007, Kim et al. 2008). This agrees with our findings about the recovery of the head tilt in a few months. Unilateral vestibular deafferentation appears to cause a slight but significant ipsilateral ocular torsion and deviation of SVH of 4—5° (Halmagyi and Curthoys 1999). In other studies, the SVH/SVV has been preoperatively 1—2°, and after VS surgery 1—5°, depending on the moment of the measurement (Hafström et al. 2004, Goto et al. 2003, Hafström et al. 2006, Parietti-Winkler et al. 2008). SVV recovered from 5° on eighth postoperative day to 1° at three months postoperative in one study, which followed VS patients serially (Parietti-Winkler et al. 2008). Thus, the head tilt in our study might also have been greater had it been measured earlier in the postoperative phase.

The oVEMP is a promising novel method for the evaluation of the functioning of otolith afferents within the superior vestibular nerve, which probably reflect the utricular function. It has even been suggested that the oVEMP might replace the caloric test in assessing the superior vestibular nerve function in patients with VS (Huang et al. 2012). The oVEMP seems to correlate with SVV and caloric responses in patients with VN (Rosengren and Kingma 2013), and might thus also correlate with head tilt. However, no data on this exist as yet.

Only half (15/30) of the patients with acute unilateral vestibular loss returned for the follow-up measurement, which must be taken into account when interpreting the results.

One shortcoming of our study with VS patients is the lack of a structured classification of the tumour origin (the superior or inferior branch of the vestibular nerve), and the degree of the intraoperative damage to the nerve. This information could have indicated whether the head tilt had been larger in patients with damage predominantly to the superior vestibular nerve. It was reported that 85% of VSs originate in the inferior vestibular nerve (Komatsuzaki and Tsunoda 2001), which suggests that the function of the saccule and the posterior SCC may probably be affected earlier than the function of the utricle, and that of the horizontal and superior SCCs. Ushio et al. (2008) found that preoperative VS patients with abnormal SVH manifested a higher number of absent caloric responses than patients with

normal SVH, which suggests that the vestibular nerve was affected more severely and/or of a broader area in patients with abnormal SVH. When the vestibular afferents are only partly affected, different vestibular tests may show inconsistent results. In an earlier study that partly included the same VS patients as in our study, the high-frequency horizontal aVOR worsened highly significantly four months after VS surgery (Hirvonen et al. 2008). This finding indicated a significant loss of SCC function, which is in contrast to that founding our study, whereby the head tilt was compensated at four months postoperatively.

6.2 MOTORIZED HEAD IMPULSE TEST

6.2.1 METHODOLOGICAL ASPECTS

Our motorized head impulse rotator provided impulses with a mean acceleration of 2050°/s², and velocity of 170°/s. The conventional way to perform the quantitative HIT is to deliver the head impulses manually. Tabak et al. (1997b) found that the reactive torque helmet-driven head impulses had more uniform acceleration compared to manually delivered impulses. The peak acceleration and velocity for the reactive torque helmet stimuli was, however, limited. Manual head impulses may vary across time, experimenters, and subjects. Indeed, the velocity and acceleration of manual head impulses have varied considerably between studies, from 80 to 400°/s, and, from 800 to 10 000°/s², respectively (Tabak et al. 1997b, Schmid-Priscoveanu et al. 2001, Lasker et al. 2002, Jorns-Häderli et al. 2007). The varying stimuli may confound comparisons of the findings between studies, or at least this aspect has to be taken into account of when interpreting such results.

Weber et al. (2008) found that the horizontal aVOR gain decreased from 0.59 to 0.29 in VN patients, and also slightly in normal subjects from 0.98 to 0.84, when the head acceleration during the quantitative HIT rose from 750 to 6000°/s². They also found that the gain reached a maximum at about 1700°/s². Very high accelerations and velocities cause a risk of slippage of the motion sensors and an increase in signal noise, in addition to the possibility of a reduction in tolerance of the test. As the video HIT is becoming more common, this should be taken into account, because the video HIT goggles are susceptible to slippage (MacDougall et al. 2009). Roy and Tomlison (2004) compared the velocity ranges for manual head impulses and found that for velocities of 200°/s or greater the results tended to be much more variable than for results for velocities under 200°/s. Although higher velocities are probably necessary in helping to reveal VOR asymmetry in patients with VN (Weber et al. 2008), lower velocities of as little as 100°/s suffice for detecting the deficit in acute patients in the video HIT

(MacDougall et al. 2009). Taking all these advantages and disadvantages of velocity settings together, we preferred our abovementioned stimulation profile with the mHIT.

The magnetic search coil has been the gold standard method used for measuring eye and head movements during quantitative head impulse testing. The technique is, however, invasive with a requirement of wearing an uncomfortable contact lens on an anaesthetized eye. In our study, the EOG was chosen for recording the eye movements in the mHIT, because it is non-invasive and is easily setup with the surface electrodes (Hirvonen et al. 2007). The disadvantages of the EOG include, a low resolution of about 1° compared to 0.02 of the magnetic search coil (Brandt and Strupp 2005), a relatively high signal-to-noise ratio that requires repeated calibration, and that the calibration itself is susceptible to vary with altering lighting conditions. During measurement, the time between the calibration and the measurement was kept as short as possible, and the room was dimly lit to avoid sources of error. The impulses with prominent noise were discarded from the analysis as it was previously found that removing individual impulses had a negligible effect on the results (Hirvonen et al. 2007). This action resulted in about 20 relatively uniform individual impulses that could be subjected to analysis.

6.2.2 PATIENTS WITH ACUTE UNILATERAL VESTIBULAR LOSS

The mean aVOR gain measured by the mHIT was substantially decreased during the acute stage of VN, while the mean contralateral gain was normal. The lowered ipsilateral gain usually improved within a few months, which is in accordance with a previous report on manual head impulses (Palla and Straumann 2004), in which the ipsilateral gain improved from an initial mean value of 0.35 to 0.55 in 10 patients measured sequentially. That same study had a somewhat different stimulation profile compared to ours, with higher peak acceleration of about 10 000°/s², and notably the amplitude of the impulses of up to 40°. The higher acceleration used in the study by Palla and Straumann (2004) directly explains their lower mean gain compared to that of ours, as discussed earlier (Weber et al. 2008). In the study by Schmid-Priscoveanu et al. (2001), the asymmetry in high-frequency VOR gain was permanently abnormal in all but one of their 14 patients when measured at least two months after VN, whereas the ipsilateral gain was below the normative range in all these patients. Their study featured, however, different patient groups for acute and chronic patients. In the studies by Schmid-Priscoveanu et al. (2001) and Palla and Straumann (2004), the patient groups were also rather small. In a more recent report that utilized video HIT and also measured the vertical canal responses, the VOR values normalized in 52% of the patients within one month (Bartolomeo et al. 2013). It should be noted that although the mean ipsilateral gain (0.79 ±

0.23) and asymmetry (12 ± 14%) in our study significantly improved during the follow-up, they both remained slightly pathological. On the other hand, the gain was normal in eight (40%) patients, and the asymmetry was normal in 13 (65%) patients at the follow-up visit. It remains unclear if the VOR function would have improved further during a longer follow-up.

The gain increase or normalization that occurred in most of the patients in our study may raise a question as to whether the recovery could be explained by the refixation saccades interfering with the eye movement recording. The earliest saccades, however, have been found to occur at approximately 150 ± 10 ms after the onset of the head movement at peak head velocities from 150 to 200°/s (Weber et al. 2008). Our velocity profile fits this range, but the peak velocities in our study were reached on average 110 ms after the onset of the head movement, which was the latest time point for the gain calculation, but which was still well before the occurrence of the early saccades. Thus, the increase in gain found in our study is unlikely to be due to the early saccades, and represents a true gain increase due to either peripheral recovery or central compensation, or both.

The asymmetry in gain in the acute stage was normal in four (13%) patients in our study. It could be argued whether these patients suffered from so-called inferior VN, which leaves the horizontal SCC function intact. The reported cases of inferior VN have, however, reported little or no spontaneous nystagmus (Aw et al. 2001, Halmagyi et al. 2002), whereas all of our patients had typical spontaneous nystagmus of peripheral origin. Central pathology was also excluded by MRI or CT scans. Our patients were measured only after their condition allowed them to tolerate the test situation, and it is possible that they had already recovered from their mild, partial vestibular loss so that their mHIT had become normal again. These patients may also have had nystagmus that was irritative in origin. For the initial evaluation of a nauseous patient in the acute stage, modern 3D-VOG evaluation may be more tolerable and also more reliable than the bedside HIT (Hirvonen and Aalto 2009).

The positive bedside HIT has been suggested to (catch-up saccades emerging when the head is turned to the lesioned side) be specific (Brandt and Strupp 2005, Halmagyi 2005, Lee et al. 2006) and sensitive to peripheral vestibular deficit, or to even confirm it (Halmagyi 2005). This suggestion has been questioned more recently after new data showed that 7—39% of patients with a stroke presenting as acute vertigo have demonstrated a false-positive bedside HIT (Cnyrim et al. 2008, Newman-Toker et al. 2008, Kattah 2009, Chen et al. 2011). Furthermore, Tarnutzer et al. (2011) found in their systematic review that a normal bedside HIT is 85% sensitive and 95% specific to central cause of vertigo. On the other hand, early (“covert”) saccades are usually unnoticed clinically, which lead to false-negative bedside

HITs in some patients (Weber et al. 2008). Tjernström et al. (2012) found that the covert saccades may become detectable by performing the bedside HIT with random amplitudes. Nevertheless, even with unpredictable and accurate head impulses in the plane of the horizontal SCC, the sensitivity of the clinical HIT has only been 71—73% (Schubert et al. 2004b, Prepageran et al. 2005). These data stress the importance of quantitative evaluation of the eye movements during the HIT. The mHIT with EOG is suitable for clinical purposes, because it provides a uniform and controllable stimulation profile, and it is able to detect a unilateral vestibular deficit as seen in our study.

6.2.3 PATIENTS WITH COCHLEAR IMPLANT

We found that four (10%) of the 41 individual CI patients had decreased postoperative ipsilateral high-acceleration aVOR gain compared to their respective preoperative value. This is in accordance of the earlier reports of 4 to 9% measured by the magnetic search coil manual HIT (Migliaccio et al. 2005, Melvin et al. 2009). However, those studies had rather small sample sizes (varying from 11 to 28 patients) and had different methodologies. The preoperative horizontal aVOR function as measured by the mHIT in our study was abnormal in 52% of the CI ears, a higher number than those of 28 to 36% reported using caloric tests (Vibert et al. 2001, Buchman et al. 2004, Melvin et al. 2009, Krause 2009, Wagner et al. 2010). The postoperative rate of patients with worsened VOR after cochlear implantation in our study is generally lower than in studies that used the caloric test, which reported rates that varied from 6 to 41% (Brey et al. 1995, Ito 1998, Buchman et al. 2004, Melvin et al. 2009, Krause 2009, Wagner et al. 2010). The low-frequency VOR results with the caloric test and high-frequency results are, however, not entirely comparable in patients with VN (Schmid-Priscoveanu et al. 2001). Furthermore, it is unclear if cochlear implantation affects the thermal conductance in the caloric test, or if the low-frequency range of the VOR is more vulnerable to surgical trauma.

Today, CI candidates have better hearing performance than before because of widened indications for implantation. This has led to taking into account the possibility of conserving residual hearing during the surgery to enable simultaneous acoustic stimulation of the preserved functioning nerve endings. With modern CIs and implantation techniques, even with full insertion of standard length electrode arrays, no significant histological intracochlear damage has been found (Briggs et al. 2006), and the preservation of hearing is also possible (Gstoettner et al. 2004, Obholzer and Gibson 2011, Helbig et al. 2011). Since most implanted ears with intracochlear damage also demonstrate damage in the vestibular end organs (Tien and Linthicum 2002), it could be assumed that hearing preservation is also associated with the preservation of vestibular function. Handzel et al. (2006) suggested that besides causing direct surgical trauma, cochlear

implantation can damage the inner ear by an inflammatory response, which affects the homeostasis of the inner ear fluid spaces, or possibly other mechanisms. In our study, the findings that the majority of the patients had impaired horizontal VOR gain in either one or usually both ears, and that the low preoperative word recognition correlated with low preoperative gain, suggest that residual cochlear and vestibular function are related to each other. The low rate for the high-frequency VOR impairment after cochlear implantation in earlier reports and in our study suggest that the implantation rarely disrupts the membranous labyrinth, at least to the extent of causing significant disturbance of the whole labyrinth function. However, because of the minor risk of permanent loss of the ipsilateral vestibular function after cochlear implantation, it is recommended that in unilateral implantation the ear with the weaker vestibular function should be preferentially implanted, when all the other factors that affect the implantation criteria are equal for both ears (Melvin et al. 2009).

A delayed loss of residual hearing has been reported by Barbara et al. (2003), who compared the residual hearing at one week postoperatively to residual hearing at up to seven years postoperatively. We found one patient who had a normal postoperative gain at the early postoperative visit to have a modestly, yet clearly decreased gain at the late postoperative visit 11 months postoperatively in our study. It is unclear if the cause for the delayed hearing impairment and vestibular loss was the surgery or due to the pathology behind the hearing impairment. In the former case: Is the mechanism the same for hearing and vestibular impairment?

6.2.4 GENERAL ASPECTS

First, Palla et al. (2008) found the correlation between the VOR function and symptoms to be poor in patients with VN. Second, Kim et al. (2008) showed that 80% of the VN patients still dizzy at the follow-up visit had a positive bedside HIT result, whereas only 10% of those patients without dizziness had a positive bedside HIT result. Third, Kammerlind et al. (2011) showed that better performance in clinical balance tests (including the Romberg test, a sharpened Romberg test, standing on a foam cushion, standing on one leg, tandem walk, and walking in a figure of 8) at the acute stage of acute unilateral vestibular loss predicted fewer symptoms six months later. We found no correlation between symptoms and objective measurements during the acute stage. At the follow-up visit, however, a modest but a significant correlation existed between the VOR function deficit and high symptom score. No strong conclusions can be made, however, until new data that investigates the varying test protocols with different clinical tools, questionnaires, length of follow-up, and patient samples emerge.

Studies with caloric tests or HIT in patients with CI have been unable to establish a correlation between decreased VOR function and vestibular symptoms (Migliaccio et al. 2005, Melvin et al. 2009, Krause et al. 2009). Those studies' findings agree with ours. In our study, none of the individual patients actually expressed a major worsening of the dizziness-related symptoms between the visits, and no significant change in the mean dizziness scores occurred during the follow-up.

7 CONCLUSIONS

1. Evaluation of head tilt and the underlying utricular function is possible with commercial VOG equipment including an integrated head position sensor. Acute unilateral vestibular deficit such as that which occurs in VN, and chronic unilateral deficit of the vestibular nerve such as that which occurs in VS often causes a slight head tilt towards the side of the lesion, which is pronounced after the head is returned to the assumed upright position after an ipsilateral tilt. The head tilt in patients with VN usually recovers over time. The surgical removal of the tumour in patients with VS has usually no significant effect on head tilting after a period of compensation.

2. The mHIT detects an acute unilateral vestibular loss in most patients as a clear asymmetry in their high-frequency aVOR gain. The peripheral function measured by the mHIT recovers fully or partially in most patients within a few months. A low gain after a few months correlates with more symptoms, and suggests that these patients may benefit from follow-up and more aggressive rehabilitation.

3. The decrease of the horizontal VOR function as measured by the mHIT is a possible but rare complication of cochlear implantation. This should, however, be taken into account when choosing the side of the implantation, and in patient counselling especially when planning bilateral cochlear implantation.

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9 APPENDIX

Questionnaire for assessing subjective sensations of the patients (in Finnish) (Studies I—IV).

Timo Hirvonen 19.9.2005

Kyselykaavake Kuulosta Ja Huimauksesta

Nimi ja sotu:_____ Pvm:_____

1. Kuuloni on

1. ========== 2. ========== 3. ========== 4. ========== 5.
Erinomainen Hyvä Kohtalainen Huono Erittäin huono

2. Minua huimaa:

1. ========== 2. ========== 3. ========== 4. ========== 5.
Harvoin Silloin tällöin Puolet ajasta Enimmäkseen Aina

3. Kun minua huimaa, oireeni on useimmiten:

1. ========== 2. ========== 3. ========== 4. ========== 5.
Erittäin lievä Lievä Kohtalainen Kohtalaisen vaikea Vaikea

4. A. Huimauksen **kesto**_____ minuuttia , ja B. **laatu**_____

(kiertävä, kaatava, keinuttava tai muu (minkälainen?)_____

5. Minkälainen on huimaukseni vaikutus päivittäisiin toimintoihin kuten työntekoon, autolla ajoon, ostoksilla käyntiin, perheestä ja itsestä huolehtimiseen?

1. ========== 2. ========== 3. ========== 4. ========== 5.
Ei vaikutusta Lievä Kohtalainen Suuri Erityisen suuri

6. Mikä on vointini vaikutus yleiseen elämänlaatuuni? Esimerkiksi sosiaalisiin aktiviteetteihin, läheisiin suhteisiin, tulevaisuuden suunnitelmiin, työn saantiin tai työssä käyntiin ja vapaa-aikaan:

1. ========== 2. ========== 3. ========== 4. ========== 5.
Ei vaikutusta Lievä Kohtalainen Suuri Erityisen suuri

7. Pelkään saavani huimausta:

1. ========== 2. ========== 3. ========== 4. ========== 5. =====>
En koskaan Harvoin Silloin tällöin Usein Aina

8. Onko vointini verrattuna viime kertaiseen käyntiini?

1. ========== 2. ========== 3. ========== 4. ========== 5. =====>
Huomattavasti huonompi Jonkin verran huonompi Samanlainen Jonkin verran parempi Huomattavasti parempi