HIGH-FREQUENCY TESTING *of the* VESTIBULAR SYSTEM

TESSA VAN DOOREN

High-frequency testing of the vestibular system

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High-frequency testing of the vestibular system

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CHAPTER 1

General introduction

General introduction

1.1. Anatomy of the vestibular system

The vestibular organ is located in the petrous portion of the temporal bone in the skull on both sides. Each vestibular organ consists of two otolithic organs and three semicircular canals. The otolithic organs (i.e., utricule and saccule) are located in the vestibule and both contain a macula. In the macula, hair cells are situated in a gelatinous mass with otoconia on top. Within the macula, a specialized curved central region is called the striola. The hair cells are orientated in different directions; mostly towards (utricule) or away from (saccule) the striola. Otoconia have a size of 0.5 to 3 µm and are inorganic crystalline deposits composed of calcium carbonate or calcite. The otoliths measure position with respect to gravity and linear acceleration. During gravity (e.g., tilting the head) or linear acceleration (e.g., motion in an elevator) position of the otoconia to the bone will change and the hair cells will be bent (and activated). The utricule is largely horizontally situated, the saccule vertically. However, as described above, their striola is a bit curved. As a result, every head movement activates and inhibits some hair cells on both sides. [1, 2] The bony semicircular canals are filled with endolymph fluid, surrounded by a membrane. Every canal has an ampulla; a widening which opens into the vestibule. In this ampulla, the cupula is situated. Within the cupula lies the sensor of the canal: the crista which contains the hair cells. When the head moves, the fluid will press against the cupula and the hair cells will be activated. In the crista, all the hair cells are all lined up in the same direction and are therefore most sensitive to movement in only one direction (the plane of the canal). Cupula deflection is in proportion to the amount of head acceleration. The density of the cupula is the same as that of the endolymph, approximately close to 1. As a result, the semicircular canals are not sensitive to gravity. The three semicircular canals are sensitive to angular acceleration, or rotation, in their planes. Their name is based on their position in the temporal bone: anterior (or superior), posterior and lateral (or horizontal). The vertical canals (anterior and posterior) are orientated 45 degrees from the sagittal plane, the lateral canal is tilted upward about 30 degrees from the horizontal plane (Figure 1). [1]

The lateral and anterior semicircular canal, together with the utricule, send head movement information to the brain mainly via the superior branch of the vestibular nerve (nervus vestibularis superior). The posterior semicircular canal and the saccule are connected to the inferior branch of the vestibular nerve (nervus vestibularis inferior). These nerves meet in the vestibular (Scarpa) ganglion and continue via the pontomedullary junction to the vestibular nuclei in the brainstem. [2] Thereafter different directions are possible to different areas of the central nervous system. Four main subdivisions of the vestibular nuclei are the superior, medial, lateral, and inferior and several minor cell groups. These

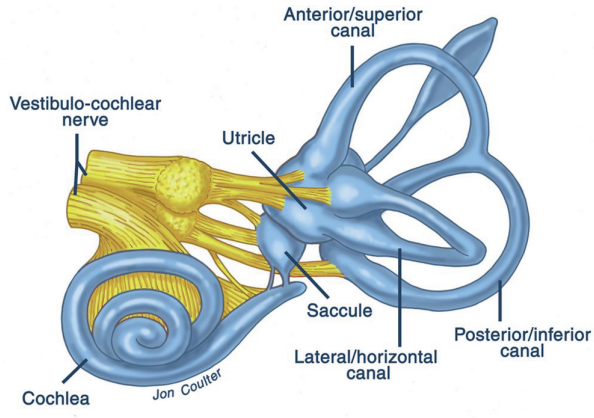

Figure 1. Basic overview of the inner ear. From https://www.earsite.com.

vestibular nuclei not only receive information directly from the vestibular organs but also (in)directly from central pathways from the cerebellum, fastigial nucleus, spinal cord, and/or visual system. The connection between the cerebellum (especially the Purkinje cells of the cerebellar flocculus) and the vestibular nuclei plays an important role in the adaptivity of the vestibulo-ocular pathways, for example in case of (sudden) vestibular loss or when wearing spectacles to correct for refractive errors. [1]

The vestibular system has different types of hair cells: type 1 (calyx fibers), type 2 (bouton fibers), and a combination of these two (dimorphic fibers). Type 1 cells contain a calyx, a special type of afferent ending that surrounds the hair cell. Therefore, they are cylindrically shaped. Type 2 cells contain a different ending and are therefore flask in shape. Type 1 cells are mostly present in the striola (of the macula) and the center of the crista (of the cupula). Type 2 cells are mostly located in the periphery of the macula and crista. Dimorphic fibers occur everywhere. These different hair cells may play different roles in encoding head movements. However, their distinctive roles are still poorly understood. [1]

The vestibular nerve afferent fibers are also classified into two types: irregular fibers (mostly type 1 hair cells) and regular fibers (type 2 hair cells), based on their (re)polarization and therefore firing rate characteristics. Irregular afferents have more excitation-inhibition asymmetry than regular afferents. Anatomically an overlap of regular and irregular fibers is found in the vestibular nuclei. It was hypothesized that the different fibers play different roles in vestibular reflexes. Possibly fast irregular fibers play an important role in Vestibulo-Ocular Reflex (VOR) adaptation (e.g., wearing corrective spectacles, sudden vestibular loss). [3]

1.2. Physiology of the vestibular system

Vestibular information is integrated into many systems of the body, such as the circadian rhythm, hemodynamic reflexes (e.g., regulation of blood pressure in different postures), and other central anatomic pathways. [4] Together with other sensory systems such as hearing, vision, and proprioception it fulfills the most important functions: image stabilization, maintaining balance and postural control, and spatial orientation. These functions are based on fundamental reflexes. [2]

Image stabilization during high frequency (>1-3Hz) head movements is controlled by the Vestibulo-Ocular Reflex (VOR). The VOR is the main parameter in vestibular testing, which will be discussed below. During walking the head moves with a frequency of around 2Hz, during running it increases to 15-20Hz. The VOR is a three-neuron reflex that runs from the vestibular organs via the superior vestibular nuclei to the eye muscles and only takes approximately 8 milliseconds. [2] To prevent retinal slip, the VOR provides an instant compensatory eye movement in the direction opposite to the head movement. [3] This reflex, like other vestibular reflexes, can adjust to new situations (like prisms or vestibular loss) to maintain image stabilization. The afferent vestibular nerves of the semicircular canals have a baseline resting firing rate of 60-80 spikes/sec. [1] The firing rate will increase at stimulation (movement towards canal) and decrease with inhibition (movement away from the canal). The range of firing rate lies between 0 and 400 spikes/ second. [5] Therefore, the extent of excitation is more than the extent of inhibition, and consequently gives the sensors a bidirectional sensitivity and an excitation-inhibition asymmetry. As a result, the canals work as functional pairs, wherein both canals are aligned in the same plane; with every movement, one canal will be excited while simultaneously the contralateral canal is inhibited. For example: when the head is rotated to the left, the left lateral semicircular canal is excited, and the right lateral canal is inhibited. The same “push-pull” function happens between the left anterior and right posterior (LARP plane), and the right anterior and left posterior (RALP plane) semicircular canal. Consequently, the three pairs of canals can uniquely specify the direction and amplitude of any head rotation. [3]

In low-frequency head movements (<1Hz), image stabilization is assured by smooth pursuit and the optokinetic response. These multisynaptic mechanisms have a longer latency than the VOR. Two other vestibular-mediated reflexes are the vestibulo-spinal and vestibulo-collic reflex. They facilitate proper head position, upright posture, and gait. Due to the relatively fast (25-250ms) and automatic response of these reflexes, balance is kept during any type of motoric task. In spatial orientation vision is the most dominant, however, the vestibular system helps to differentiate (e.g.: it can be challenging to discriminate between self-motion and environmental motion when sitting in a train and the train next to you departs).

1.3. Bilateral Vestibulopathy

Patients with Bilateral Vestibulopathy (BV) have an impaired or absent vestibular function on both sides. [6] Unlike blindness (loss of vision) or deafness (loss of hearing), there is no word for bilateral loss of vestibular function. Prevalence in literature is between 28 and 81 in 100.000 adults. Due to under- and misdiagnosis of BV, this is probably an underestimation. [7] BV is a heterogeneous disorder with a wide variety of clinical symptoms. The most described complaints comprise unsteadiness, visual problems (oscillopsia, visual vertigo, or trouble with reading), not being able to perform fast head movements, tiredness, trouble with double tasks, and problems with spatial orientation (i.e., disorientating problems and misjudging distance). Darkness and uneven grounds worsen these symptoms. Patients experience problems in busy environments (e.g., supermarkets). Activities are often performed more slowly, with more attention, or are completely avoided. As a result, more energy is consumed, and/or patients become more socially isolated. [7] Vestibular hypofunction is associated with a negative impact on quality of life and an increase in health care costs. [8]. In half of the patients, the underlying etiology remains unclear. Many etiologies are possible, including: ototoxicity; infection; auto-immunity; neurodegeneration; hereditary; vascular; neoplastic; trauma; syndromal. [9] Currently, no effective treatment to restore peripheral vestibular function is available for BV patients. [10] However, an artificial balance organ, the Vestibular Implant, has been shown to restore vestibular reflexes and could be a possible treatment option in the (near) future. [11]

1.4. High-frequency testing of the vestibular system

Different frequency sensitivities of the vestibular system can be tested, similar to audiometry when testing hearing function. The lower and middle frequencies of the semicircular canals can be tested by the caloric test and rotatory chair testing. The higher frequencies of the semicircular canals can be tested by several tests which will be discussed below. The function of the otoliths can be assessed using cVEMP and/or oVEMP testing (cervical and ocular vestibular evoked myogenic potential). The latter is beyond the scope of this thesis.

1.4.1. The Head Impulse Test (HIT, or HIMP)

The Head Impulse Test (HIT, or HIMP) is a clinical “bedside” test that does not require any equipment. During this test, the examiner applies head impulses to the test subject, which comprise fast (>120°/s) passive head movements with a small amplitude (10-30°), unpredictable in timing and direction. Subjects are asked to fixate on an earth-fixed target at eye level in front of them (mostly the nose of the examiner). In the case of a normal VOR, the eyes will immediately move in the contralateral direction of the head impulse, to assure gaze stability (i.e., the eyes stay on the target). In patients with a deficient VOR, the eyes

will move slower than the head, or even initially move along with the head. To correct for the loss of gaze, a compensatory eye movement (saccade) is necessary to refixate on the target. Thus, the appearance of these saccades indicates vestibular hypofunction. Saccades can appear after (i.e., overt saccade) or during (i.e., covert saccade) the head impulse. Overt saccades are often detected by the naked eye of the examiner. However, this is more challenging for covert saccades.

1.4.2. The Video Head Impulse Test (VHIT)

To better quantify head impulse testing, the Video Head Impulse Test (VHIT) was introduced in 1991. [12] This device tracks head and eye movements during the head impulse test and is, therefore, able to detect overt and covert saccades. Different types of VHIT devices are commercially available, including systems with head-mounted lightweight goggles or an earth-fixed remote camera. The main outcome parameter is VOR gain, calculated as the ratio between eye and head movement. VOR gain will be close to 1 in healthy subjects and lower in patients with a deficient VOR. For example, a horizontal VOR gain of <0.8 is classified as pathological, and a bilateral VOR gain of <0.6 is classified as bilateral vestibulopathy (BV). [6] Different systems use different algorithms to calculate VOR gain. For example, the algorithm using “area under the curve” calculates VOR gain as the ratio of the area under the eye velocity and head velocity curve during the head movement, while the algorithm using “instantaneous gain” divides eye- and head velocity at a certain point in time or at a certain point of acceleration. Covert saccades might challenge VOR gain calculation due to their interference with eye movements produced by the VOR. Current VHIT systems try to (partially) overcome this issue by, for example, desaccading the eye movements.

1.4.3. The Suppression Head Impulse Test (SHIMP)

The Suppression Head Impulse (SHIMP) test was proposed as an alternative, to overcome challenges in VOR gain calculation due to possible interference of covert saccades. [13] The test setup is similar to the other VHIT tests, but the main difference is the target being head-fixed (a laser dot projected by the lightweight goggles) instead of being earth-fixed (e.g., a dot on the wall). Therefore, the target moves along with the head during the impulse. In case of an adequate VOR, the eyes will initially move in the contralateral direction of the head. However, since the target is head-fixed, healthy subjects need compensatory eye movements (saccades) to bring the eyes back on the target. When the test is performed correctly, these saccades will mainly occur after the head impulse (overt saccades), and not during the head impulse (covert saccades). Therefore, with SHIMP, a compensatory saccade indicates the vestibular function, while a compensatory saccade during HIMP indicates a vestibular loss. It was hypothesized that this elimination of covert saccades during SHIMP might facilitate a more precise VOR gain calculation than in HIMP.

1.4.4. The Functional Head Impulse Test (fHIT) and Dynamic Visual Acuity (DVA)

The functional Head Impulse Test (fHIT) and Dynamic Visual Acuity test (DVA) are complementary to VHIT. VHIT quantifies VOR function, while fHIT and DVA measure the functional performance of the VOR (i.e., visual stabilization abilities). Regarding fHIT, the test setup is similar to VHIT, only the target is an optotype that only appears on the screen during the head impulse. The subject has to choose the right optotype out of eight different options by pressing the corresponding button on the keyboard. In case of a deficient VOR without useful saccades, the subject might not be able to identify the optotype correctly. The percentage of correct answers is considered the outcome of the test. [14] Regarding DVA, various clinical testing paradigms have been proposed to assess DVA, like walking on a treadmill ($DVA_{treadmill}$) or passively shaking the head, while reading an optotype chart. During the $DVA_{treadmill}$ patients have to walk on a treadmill at different walking speeds (e.g., 0km/h (standing still), 2km/h, 4km/h, and 6km/h) while reading Sloan optotypes (CDHKNORSVZ) of decreasing size. This is continued until the subject does not recognize more than 10% of the letters (chance rate). The difference between recognized optotype size when standing still and walking is the outcome of the test. [15] Possibly, fHIT and DVA outcomes might correlate with the complaints of oscillopsia in patients with vestibular loss. Oscillopsia can subjectively be quantified by questionnaires, such as the Oscillopsia Severity Questionnaire (OSQ). [16] These questionnaires were designed to classify the disease burden experienced by patients in daily life. It should be noted that no gold standard is available subjectively measure oscillopsia.

1.5. Outline of this thesis

Chapter two: The Video Head Impulse Test (VHIT) and the influence of daily use of spectacles to correct a refractive error

The VOR is adaptive and can be changed by wearing prisms or magnification glasses. Therefore, wearing corrective spectacles might also influence VOR gain during (video) head impulse testing. If this would be the case, all future VHIT testing might need to correct for this effect. In this chapter, VHIT outcomes are compared between subjects wearing corrective spectacles to compensate for a refractive error (between -10 and 10 Diopter), a control group of subjects wearing contact lenses, and a group of healthy subjects with normal vision. Furthermore, VHIT outcomes can be influenced by artefacts. To obtain reliable outcomes, it is important to have a standardized setup and an experienced examiner. This chapter describes the experimental setup which was used in all other chapters of this thesis. It also became part of routine clinical care of the Vestibular Laboratory in the MUMC+.

Chapter three: Comparison of three video head impulse test systems for the diagnosis of bilateral vestibulopathy
Different commercial VHIT systems are available. Previous studies in healthy subjects did not find any differences in VHIT outcomes between different VHIT devices. However, this was not tested in a large group of patients with BV. This chapter compares VHIT outcomes of BV patients, obtained with three different commercially available VHIT devices.

Chapter four: Suppression Head Impulse test (SHIMP) versus Head Impulse test (HIMP) when diagnosing Bilateral Vestibulopathy
As stated above, BV patients might produce covert saccades during VHIT testing, which can interfere with VOR gain calculations. SHIMP was introduced to overcome this issue by reducing covert saccades. This chapter compares SHIMP and HIMP outcomes in a large group of BV patients and investigates the additional value of using SHIMP in BV.

Chapter five: The functional Head Impulse Test (fHIT) to assess dynamic visual acuity and oscillopsia in patients with Bilateral Vestibulopathy
VHIT quantifies the VOR but does not objectify the functional performance of the VOR, in contrast to fHIT and DVAtreadmill. This chapter compares fHIT and DVAtreadmill outcomes with Oscillopsia Severity Questionnaire results in a group of BV patients.

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CHAPTER 2

The Video Head Impulse Test (VHIT) and the influence of daily use of spectacles to correct a refractive error

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Abstract

Objective: To determine the influence of daily use of spectacles to correct a refractive error, on the VOR gain measured with the video head impulse test (VHIT).

Study design: This prospective study enrolled subjects between 18 and 80 years old with and without a refractive error. Subjects were classified into three groups: (1) contact lenses, (2) spectacles, and (3) control group without visual impairment. Exclusion criteria comprised ophthalmic pathology, history of vestibular disorders, and alternated use of spectacles and contact lenses in daily life. Corrective spectacles were removed seconds before testing. One examiner performed all VHITs under standardized circumstances using the EyeSeeCam system. This system calculated the horizontal VOR gain for rightward and leftward head rotations separately.

Results: No statistically significant difference was found in VOR gain between the control group (n=16), spectacles group (n=48) and contact lenses group (n=15) (p=0.111). Both the spectacles group and contact lenses group showed no statistically significant correlation between VOR gain and amount of refractive error, for rightwards (p=0.071) and leftwards (p=0.716) head rotations. There was no statistically significant difference in VOR gain between testing monocularly or binocularly (p=0.132) and between testing with or without wearing contact lenses (p=0.800).

Conclusion: In this study, VOR gain was not influenced by wearing corrective spectacles or contact lenses on a daily basis. Based on this study, no corrective measures are necessary when performing the VHIT on subjects with a refractive error, regardless of the way of correction.

1. Introduction

The vestibulo-ocular reflex (VOR) enables gaze stabilization during head movements with an instant compensatory eye movement in the direction opposite to the head movement [1]. The VOR can be used to assess vestibular function [2]. A test to examine the VOR in the high-frequency domain is the Head Impulse Test (HIT). The HIT comprises a passive, unpredictable, low-amplitude, rapid head rotation, performed by an examiner, while the patient maintains a gaze on a target [2] [3] [4]. In case of a peripheral vestibular loss, the eyes will not be able to maintain a gaze on the target and are forced to make a compensatory catch-up saccade. Saccades can occur after the head movement ("overt" saccades), or during the head movement ("covert" saccades). Even for experts, covert saccades are often undetectable by the naked eye during the manual HIT [5] [6] [7].

Covert saccades can be detected by the Video Head Impulse Test (VHIT). This test uses a lightweight video-oculography device with a high-speed infrared video camera while performing the HIT. The camera tracks head and pupil movement during the head impulse and therefore detects both overt and covert saccades [8]. The VHIT is a validated method to assess peripheral vestibular dysfunction in the high-frequency domain [9] [10]. Unlike the scleral coil method, it is noninvasive and easy for clinical use [7] [11]. At this moment, the vestibulo-ocular reflex gain (VOR gain) is considered to be the main outcome parameter to measure performance. It represents the correlation between eye velocity and head velocity and can be calculated in various ways [4] [8] [12] [13] [14].

Regardless of the way of calculation, the VOR gain is influenced by eye movements. When wearing optical devices, the eye movement will change to assure gaze stabilization. This mechanism can be so extreme that a total reversal of the direction of the VOR was observed during a study with dove prisms [15]. A more modest change takes place when wearing spectacles to correct a refractive error. Due to the prims effect of the glass, objects are viewed in a different line of sight than the principal axis of the lens of the eye. This means, in comparison to 'normal' vision, a bigger or smaller eye movement is needed to maintain gaze stabilization while wearing corrective spectacles. The difference in eye movement depends on the diopter of the glass [1]. A bigger or smaller eye movement during the same head movement means a smaller or bigger VOR gain value.

In this study, it was hypothesized that the VOR gain, as measured with the VHIT, could be influenced by wearing spectacles on a daily basis to correct a refractive error. Wearing contact lenses would not influence VOR gain to any degree because the contact lenses rotate along with the eyes and therefore have no prism effect [1] [16]. This hypothesis might imply when testing VOR gain with VHIT in subjects with a refractive error, corrective

measures should be made to prevent false diagnosis of vestibular dysfunction, depending on the way of correction.

2. Material and methods

This study determined the influence of daily use of spectacles to correct a refractive error, on the VOR gain measured with the VHIT. Subjects wearing spectacles were compared to subjects without visual impairment and subjects wearing contact lenses.

2.1. Study population

A prospective study was performed on volunteers in optician stores in Maastricht. These settings were chosen to precisely determine the diopter in the worn spectacles and contact lenses for each subject. Subjects met the following inclusion criteria: 1) age between 18 and 80 years old, 2) presence of refractive error, and 3) wearing corrective spectacles or contact lenses on a daily basis. Subjects were excluded when they 1) alternated between glasses and contact lenses during daily life or when they 2) were unable to see the point of fixation for the VHIT. Further exclusion criteria comprised 3) ophthalmic pathology or surgery, 4) neck pathology, 5) history of vestibular disorders, and 6) a difference in refractive error between both eyes of more than 4 Diopter.

The same exclusion criteria were applied to the control group, which comprised healthy volunteers between 18 and 80 years old with no visual impairment. Informed consent was obtained before testing.

2.2. Protocol

The VOR gain can be influenced by artifacts resulting from goggle slippage, incorrect calibration, imperfect pupil tracking, blinking, head overshoot, touching goggles, patient inattention, and target distance [8] [14] [17] [18] [19]. To reduce these artifacts to a minimum, a strict testing protocol was designed by all authors and used by the examiner, as described below.

2.2.1. Experimental setup

The examiner (TD) ensured a constant distance of 2 meters from the back of the chair to the point of fixation. A static chair was used to prevent body movement during testing. The point of fixation consisted of a laser on a tripod, pointing a green dot on a white wall to create maximum contrast. The examiner adjusted the fixating point to the eye level of the subject. The light intensity was measured with an illuminance meter, and the light intensity

at the focusing point in the room was kept between 80 and 320 lux. This ensured a small pupil in every subject and therefore facilitated a wider range for measuring eye movements. At the same time, it minimized the change of artifacts due to light reflection onto the pupil.

2.2.2. VHIT preparations

Since the amount of refractive error could differ between the eyes, the subject's left eye was covered with a sticker before the goggles were applied. By this, only the right eye was measured. As the Diopter of the correction (spectacles/contact lenses) influences the VOR, this value was used for inclusion, rather than the refractive error itself. Goggle movement was minimized by adjusting the strap of the goggles to every subject. The camera was focused on the pupil while the subject looked at the point of fixation with eyes wide open. In case the eyelids were in front of the pupil, the examiner adjusted the rim of the goggles so they would hold the eyelids back. A five-point laser grid, mounted on the goggles, was used to calibrate the EyeSeeCam system (EyeSeeCam VOG; Munich, Germany). It projected a red luminous dot pattern on the wall. The examiner instructed all subjects to look at five dots in the same order without moving their head. When vision was too impaired to see the red dots, the subjects were instructed to follow the examiner's finger while the examiner pointed out these dots. The examiner assessed the quality of the calibration and determined whether the process needed to be repeated. After calibration, the subject was instructed to not touch (the strap of) the goggles, their face, and/or their hair.

2.2.3. VHIT

One trained examiner (TD) performed the horizontal VHIT on every subject. The examiner stood behind the subject with both hands on top of the head, holding it firmly without touching the strap or goggles. Before the start of official testing, slow horizontal sinusoidal head movements were given to assess neck stiffness and to give final instructions. Subjects were instructed to relax their neck, keep their eyes wide open, and fixate on the target in front of them. The examiner continuously repeated these instructions to facilitate optimal awareness of the subject. The head impulses comprised fast (peak velocity >150°/s) horizontal rotational head movements with low amplitude (+/-20°), unpredictable in timing and direction [14]. Only outward impulses were used [20].

2.2.4. Testing paradigm

One recording session consisted of two trials with at least 10 impulses to each side in total. Every trial resulted in two VOR gain values as the outcome, one for the head movement to the right and one for the head movement to the left. In total, every recording session consisted of four VOR gain values. A stopwatch was used to time every recording session.

Subjects in the spectacles group underwent one recording session: without wearing their spectacles. Subjects in the contact lenses group underwent two recording sessions: with and without wearing contact lenses. This way, it was possible to evaluate the influence of wearing contact lenses during the VHIT. Subjects in the control group underwent three recording sessions: the first and third recording sessions were performed binocularly, and the second session was performed monocularly with the left eye covered. This setup was used to determine the reproducibility of the trials and to determine the difference in outcomes between monocular (left eye covered) and binocular (no eye coverage) testing. All recording sessions were sequentially performed. Table 1 shows an overview of the testing paradigm as described above.

Table 1. Overview of the testing paradigm

Group 1: Spectacles				
Trial 1	VOR gain R VOR gain L	*Trial 2*	VOR gain R VOR gain L	= *Recording session 1*: testing without wearing spectacles
Group 2: Contact lenses				
Trial 1	VOR gain R VOR gain L	*Trial 2*	VOR gain R VOR gain L	= *Recording session 1*: testing while wearing contact lenses
Trial 3	VOR gain R VOR gain L	*Trial 4*	VOR gain R VOR gain L	= *Recording session 2*: testing without wearing contact lenses
Group 3: Control				
Trial 1	VOR gain R VOR gain L	*Trial 2*	VOR gain R VOR gain L	= *Recording session 1*: binocular testing
Trial 3	VOR gain R VOR gain L	*Trial 4*	VOR gain R VOR gain L	= *Recording session 2*: monocular testing (left eye covered)
Trial 5	VOR gain R VOR gain L	*Trial 6*	VOR gain R VOR gain L	= *Recording session 3*: binocular testing

Group 1 (spectacles) underwent one recording session: without wearing their spectacles. Group 2 (contact lenses) underwent two recording sessions: with and without wearing their contact lenses. All recording sessions in Groups 1 and 2 were performed monocularly (with the left eye covered). Group 3 (control group) underwent three recording sessions: the first and third recording sessions were performed binocularly (without eye coverage) and the second session was performed monocularly (left eye covered). One recording session consisted of two trials with at least 10 impulses to each side in total, tested under the same conditions. R = rightwards head impulse. L = leftwards head impulse.

2.3. Data analysis

The shapes of all traces were assessed in consensus by three of the authors (TD, FL, RB). To detect artifacts and look for a possible correlation between artifacts and refractive error, data was blinded. During analysis, two trials of the same recording session were kept together as a pair. Every pair of trials was placed in one of the following subgroups: (1) phase lead (eyes peak velocities appeared >20ms earlier than head peak velocity), (2) phase

lead with overt saccades (≥50% of all the impulses on one side showed overt saccades), (3) small overt saccades (>50% of the overt saccades were slower than 100°/s), (4) large overt saccades (>50% of the overt saccades were faster than 100°/s), (5) backward overt saccades (overt saccades went into opposite direction), (6) noise (traces were not completely smooth but did not have saccades) and (7) normal. Only phase lead was considered to be an artifact that could influence VOR gain and for this reason, subjects with a phase lead were excluded.

The EyeSeeCam software (*revision r3448M, April 2016*) backed by Matlab scripts were used for data analysis.

2.4. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 23. Normality was checked by the Shapiro-Wilk test and visual inspection of the outcome distribution. Where multiple comparisons were made, the Bonferroni adjusted p-values are given and compared to a standard p-value of 0.05. The VOR gain of every trial was calculated by the EyeSeeCam software for rightward and leftward head impulses separately. The Chi-square test and one-way analysis of variance (ANOVA) were used to evaluate the homogenous nature of the groups (gender and age).

To evaluate the test-retest reliability as the consistency between the repeated measures of the same outcome condition, two-way random intraclass correlation coefficients (ICC) were calculated for the repeated trials within one recording session [21]. A two-way repeated-measures ANOVA with 2 within-subject factors (side (left/right) and monocular testing (yes/no) or testing with contact lenses (yes/no)) was used to detect a statistically significant difference in testing monocularly (left eye covered) or binocularly (no eye coverage) and testing with or without wearing contact lenses.

The difference in VOR gain between the groups was analyzed with ANOVA repeated measures with 1 within-subject factor (side) and 1 between-subject factor (group).

A regression analysis was used to determine the effect of Diopter and group (spectacles/contact lenses) on the VOR gain.

2.5. Ethical considerations

This study was performed following the guidelines outlined by Dutch legislation. According to the Medical Research Involving Human Subjects Act (WMO) ethical approval was not required, since the purpose of this study was to validate our system and to obtain the normative values.

3. Results

In total 79 subjects were included (Table 2). No significant difference was found in gender. A statistically significant age difference was found between the spectacles group and the control group (p=0.005). Subjects were wearing corrective spectacles for at least 4 months, up to 60 years.

Table 2. Baseline characteristics of the study population

Characteristics	Spectacles	Contact lenses	Control	All
N	48	15	16	79
Male	26	5	7	38
Female	22	10	9	41
Mean age in yrs. [SD]	54 [17]*	43 [10]	39 [14]*	48 [16.5]

*A statistically significant difference in age between the spectacles group and the control group (p=0.005).

The first trial of the VHIT started within 90-300 seconds after the removal of the correction. One recording session (Table 1) did not take longer than 480 seconds.

During a visual assessment of the VHIT graphs, no covert saccades were observed and no causality was seen between refractive errors and the shape of the traces (as classified into the subgroups).

The trials within one recording session (Table 1) showed a good test-retest reliability, the intraclass correlation coefficient varied between 0.707 (p=0.012) and 0.959 (p=0.000).

There is no statistically significant difference in VOR gain between testing monocular (left eye covered) or binocular (no eye coverage) ($F(1,15)=2.538$, $p=0.132$), between testing with or without wearing contact lenses ($F(1,14)=0.067$, $p=0.800$) and between rightwards and leftwards head rotations ($F(1,76)=2.370$, $p=0.128$).

The VOR gain was compared between the spectacles group, contact lenses group, and control group. No statistically significant difference was found in VOR gain between these groups ($F(2,76)=2.265$, $p=0.111$). Regarding the VOR gain for different Diopter, no significant interaction was found between group (spectacles/contact lenses) and Diopter for rightwards ($p=0.376$) and leftwards ($p=0.189$) head rotations. The spectacles group tended to show a positive relationship between refractive error and VOR gain, but both in the spectacles group and contact lenses group no statistically significant correlation was found between VOR gain and different Diopter, for rightwards ($p=0.071$) and leftwards ($p=0.716$) head rotations.

Compared to the control group, VOR gain measured by the VHIT is not influenced by refractive error and daily use of spectacles or contact lenses (Figure 1).

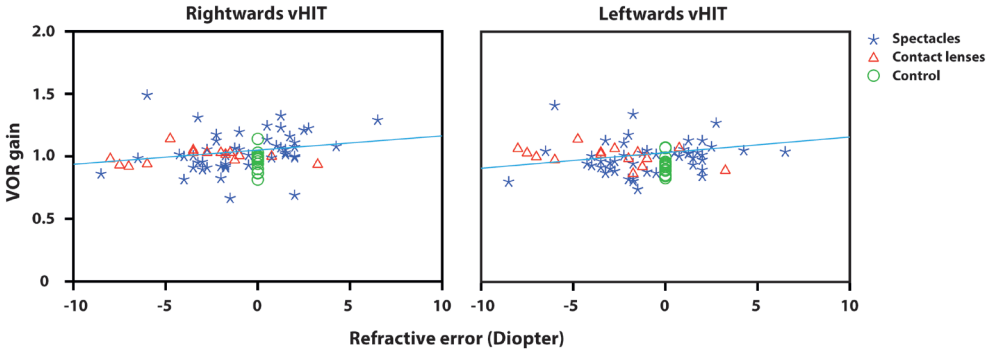

Figure 1. VOR gain plotted against refractive error for right- and leftwards head impulses. Every symbol represents the VOR gain of one subject calculated by the EyeSeeCam system. VOR gain did not differ significantly between the groups (spectacles, contact lenses, control group). No statistically significant correlation was found between VOR gain and different Diopter in both the spectacles group and contact lenses group for rightwards and leftwards head rotations. The regression line shows a tendency of a positive relationship between refractive error and VOR gain, but the difference is negligible and has no clinical significance.

4. Discussion

To our knowledge, this is the first study to determine the influence of daily use of spectacles to correct a refractive error on the VOR gain measured by the VHIT, on a study population of this size. This study showed no statistically significant correlation between VOR gain and the amount of refractive error and no significant difference was found in VOR gain between the groups (corrective spectacles, contact lenses, and control group without visual impairment). The spectacles group tended to show a positive relationship between refractive error and VOR gain, but the effect size is negligible. This means VHIT is not influenced by Diopter or the way it is being corrected in daily life. Therefore, based on this study, no special measures are necessary when performing the VHIT on subjects with a refractive error.

Although this study illustrates that VOR gain is not influenced by a refractive error, regardless of the Diopter and way of correction, other studies did show VOR gain changes when exposed to sensory rearrangement such as magnifying spectacles or prisms [15] [17] [22] [23] [16] [24]. The differences could be partly explained by the methods. Firstly, none of the studies tested the VOR gain by using the VHIT. This implies that other methods were used that investigated different frequencies. Secondly, in some studies, subjects were tested in the dark or whilst wearing the temporary sensory rearrangements, contrary to our subjects.

However, the discrepancy between this study and other studies could mainly be explained by two theories about centrally regulated mechanisms, as will now be described. The first mechanism is dual-state adaptation. Dual state adaptation means the ability to switch between different states, for instance, between vision with corrective spectacles and normal vision (without sensory rearrangements). This adaptive process is enhanced by repeated exposure and results in adapting and readapting within seconds. In previous studies, subjects were exposed to the sensory rearrangement for only one or two periods of 40 minutes to a maximum of 4 weeks and tested immediately after. Our study population had been wearing corrective spectacles for at least 4 months, up to 60 years. It might be possible that these well-exposed subjects benefited from an enhanced dual state adaptation and were already readapted to vision without their spectacles within the 90 to 300 seconds between removal of the correction and start of the VHIT. As a result, no VOR gain change could be measured by the VHIT [22] [16] [24] [25] [26] [27]. The second theory could be central compensation by the brain. For example: in the case of aniseikonia [a large difference in refractive error between both eyes] the brain can compensate for the distorted images projected on the retina. The same compensation could be happening while wearing corrective spectacles. This would imply that the VOR would not change while wearing corrective spectacles and therefore will not influence the VOR gain as measured by the VHIT [28].

Regarding testing methods, no difference was found in VOR gain between monocularly and binocularly testing, and between testing with and without wearing contact lenses. Furthermore, it showed good reproducibility of the VHIT. This implies that VOR gain is not influenced by monocular testing, wearing contact lenses, and repeatedly testing the VHIT.

This study showed a nonsignificant difference in VOR gain between rightwards en leftwards head rotations. At high head impulse accelerations, it was shown that the latency of the adducting eye is longer than the latency of the abducting eye accompanied by on average 15.3% higher gains of the adducting than gains of the abducting eye [30]. As described in the methods, for practical reasons we choose to detect and compare only eye movements of the right eye and only varied the visual fixation conditions during the head impulses (monocular or binocular fixation, with or without contact lenses). This implies that we anticipated a maximum 15.3% higher gain of the VOR of the fastest impulses to the right.

One limitation of this study is the fact that the subjects in the control group were younger than the subjects of the spectacle group. Articles showed no VOR gain change until the age of 80 years, which means that it should not influence the outcome of this study, since subjects older than 80 years were excluded [3] [20] [29].

5. Conclusion

Based on this study, corrective measures are not necessary when performing the VHIT on subjects with a refractive error, regardless of the way of correction.

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CHAPTER 3

Comparison of three Video Head Impulse Test (VHIT) systems for the diagnosis of Bilateral Vestibulopathy

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Abstract

Introduction: A horizontal vestibulo-ocular reflex gain (VOR gain) of < 0.6, measured by the video head impulse test (VHIT), is one of the diagnostic criteria for bilateral vestibulopathy (BV) according to the Bárány Society. Several VHIT systems are commercially available, each with different techniques of tracking head and eye movements and different methods of gain calculation. This study compared three different VHIT systems in patients diagnosed with BV.

Methods: This study comprised 46 BV patients (diagnosed according to the Bárány criteria), tested with three commercial VHIT systems (Interacoustics, Otometrics, and Synapsys) in random order. The main outcome parameter was VOR gain as calculated by the system, and the agreement on BV diagnosis (VOR gain <0.6) between the VHIT systems. Peak head velocities, the order effect, and covert saccades were analysed separately, to determine whether these parameters could have influenced differences in outcome between VHIT systems.

Results: VOR gain in the Synapsys system differed significantly from VOR gain in the other two systems ($F(1.256, 33.916)=35.681$, $p<0.000$). The VHIT systems agreed in 83% of the patients on the BV diagnosis. Peak head velocities, the order effect, and covert saccades were not likely to have influenced the above-mentioned results.

Conclusion: To conclude, using different VHIT systems in the same BV patient, can lead to clinically significant differences in VOR gain when using a cut-off value of 0.6. This might hinder the proper diagnosis of BV patients. It would therefore be preferred that VHIT systems are standardized regarding eye and head tracking methods, and VOR gain calculation algorithms. Until then, it is advised to not only consider the VOR gain when assessing a VHIT trial but to also look at the raw traces and the compensatory saccades.

1. Introduction

Bilateral Vestibulopathy (BV) is a heterogeneous chronic condition in which the vestibular function is severely impaired or absent in both ears. [1] A greatly reduced or absent vestibulo-ocular reflex (VOR) is a main clinical marker of BV, among other symptoms. [2] To quantify the VOR function in all planes of the semicircular canals, the video head impulse test (VHIT) is widely used. [3] The vestibulo-ocular reflex gain (VOR gain) is considered to be the main outcome parameter of the VHIT. VOR gain represents the relationship between the eye and head velocity and can be calculated in various ways. For example, VOR gain can be calculated as the ratio between eye and head velocity at a certain point in time, at peak head velocity, or throughout the whole head movement (i.e., the area under the curve gain, regression analysis). [4-6] VOR gain should be close to 1.0 in healthy subjects. [7] Therefore, a decreased VOR function should result in a decreased VOR gain. Moreover, a horizontal angular VOR gain of <0.6 on both sides, as measured by the VHIT, is one of the diagnostic criteria for BV according to the Bárány Society. [8]

BV patients can also show catch-up saccades during the VHIT. These saccades are a compensation mechanism for the retinal slip during head movements and can occur during or shortly after a head impulse (“covert” saccades and “overt” saccades respectively). As an adaptation effect, the latency of the catch-up saccades can decrease and therefore the number of covert saccades can increase. [9] These covert saccades could influence VOR gain calculations, especially when the area under the curve gain calculation is used.

Several VHIT systems are commercially available, each with different methods of gain calculation and different techniques of tracking eye and head movements. Small study populations show significant differences in VOR gain between different VHIT systems within healthy subjects and patients. Despite these differences in VOR gain, all systems identified vestibular deficits similarly. [5, 6] It is unknown what the effect of using different VHIT systems is on the VOR gain in subjects with severely impaired vestibular function in both ears. In case the use of different VHIT systems would result in different clinical diagnoses within the same patient (e.g., classifying a patient as “yes” or “no” with BV), it might be necessary to standardize systems regarding VOR gain calculation algorithms and eye and head tracking methods.

The objective of this study was to compare three commercial VHIT systems (Interacoustics, Otometrics, and Synapsys) in a large group of BV patients. The main outcome parameters were horizontal VOR gain as calculated by the system, and the agreement between the systems on identifying BV according to the diagnostic criteria (horizontal VOR gain <0.6). Since there are technological differences inherent to the VHIT systems (i.e., different VOR

gain calculation algorithms and different head and eye-tracking), it was hypothesized that different VHIT systems could lead to clinically relevant differences in VHIT outcomes within the same BV patient.

2. Methods

2.1. Study population

This study comprised 46 patients diagnosed with BV at the Division of Balance Disorders at Maastricht University Hospital, based on the diagnostic criteria for BV from the Bárány Society. [8] Since VOR gain obtained by VHIT was used as an outcome parameter in this study, this criterium was removed from the inclusion criteria. Patients diagnosed with BV solely based on VHIT outcomes were therefore not part of this study population. Inclusion criteria comprised 1) reduced caloric response (sum of bithermal maximum peak slow phase eye velocities of <6 °/s on each side), 2) and/or reduced horizontal angular VOR gain <0.1 on the rotatory chair and a phase lead >68°. Exclusion criteria comprised being unable to stop vestibular suppressants for one week (cinnarizine and all psychiatric medication), and the inability to undergo one of the vestibular examinations.

2.2. Testing protocol

2.2.1. Experimental setup [7]

One trained examiner (FL) performed all VHITs. A fixed distance of two meters from the back of the chair to the point of fixation was ensured. [10] Patients were seated on a static chair, to prevent upper body movement during head impulses. The room was well lit, to ensure a small pupil in every patient. Patients fixated on a green (532nm) 1 mw laser dot projected on a large full visual field black (or white) painted wall. This facilitated a wider range for measuring eye movements. At the same time, it minimized the change of artefacts due to light reflections onto the pupil. The fixating point was adjusted to the eye level of every patient. Each test started with the calibration of the system. The examiner assessed the quality of the calibration and determined whether the process needed to be repeated. The examiner stood behind the patient, holding the head firmly during head impulses. Patients were instructed to relax their necks, keep their eyes wide open, and fixate on the target in front of them. The examiner continuously repeated these instructions to facilitate optimal awareness of the patient. The head impulses comprised fast horizontal rotational head movements (>120°/s) with a low amplitude, unpredictable in timing and direction. Only outward impulses were given. [11]

The camera of the Interacoustics and Otometrics systems is head-fixed and is integrated into a pair of goggles. Therefore, before the start of testing, goggle movement was minimized by tightly fastening the strap of the goggles around the patients' head. The camera was always set on the right eye and focused on the pupil while the patient looked at the point of fixation with eyes wide open. In case the eyelids were in front of the pupil, the examiner adjusted the rim of the goggles so they would hold the eyelids back. After calibration, the patient was instructed to not touch (the strap of) the goggles, their face, and/or their hair. The camera of the Synapsys system is space-fixed, and therefore no goggles were used. The camera that measured eye and head movements were placed in front of the patient. Eye movements from both eyes were measured (Figure 1).

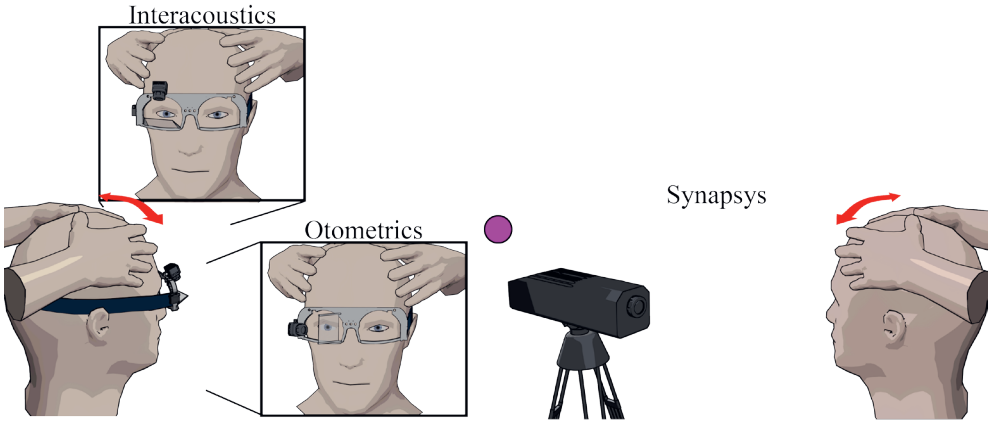

Figure 1. Animations of the three VHIT systems used in this study. The Interacoustics and Otometrics VHIT systems both consist of a pair of goggles with a built-in eye and head movement tracking system. The Synapsys VHIT system comprises a space-fixed camera placed in front of the patient.

2.2.2. VHIT systems

Three different VHIT systems were used in this study: EyeSeeCam (Interacoustics VOG; Munich, Germany), ICS Impulse (GN Otometrics; Taastrup, Denmark), and Ulmer (Synapsys, Marseille, France). Each patient sequentially underwent the horizontal VHIT with the different VHIT systems. The Synapsys system was not used in 17 patients, and the Interacoustics system was not used in one patient, due to the unavailability of the systems at the time of testing. The order of testing of the different VHIT systems was randomized by draw.

2.3. VOR gain calculation by the different VHIT systems

VOR gain, as calculated by the systems, was used as the main outcome parameter. The three systems calculate VOR gain differently. Interacoustics uses instantaneous gain; it divides eye- and head velocity at a certain point in time (a small window around 60 ms) after the onset

of the head movement. [12] Otometrics calculates VOR gain as the ratio of the area under the eye velocity and head velocity curve (from 60 ms before peak head acceleration to the last value of 0°/s as the head returns to rest). If needed, the eye movement is desaccaded by the system before the VOR gain is calculated. [13] The Synapsys system calculates the VOR gain over the period from 40 ms before to 80 ms after peak head acceleration for each impulse. In the case of a covert saccade, the 80 ms window is reduced and stops at the time of onset of the covert saccade. [14] However, the method of gain calculation used by the Synapsys system was unknown to this research group, despite multiple efforts to obtain more information from the manufacturer.

2.4. Covert saccades

Covert saccades might influence VOR gain (calculation). Therefore, covert saccades in this study population were analysed separately to assess whether they differed between tests (as an adaptation effect) in this BV population when repeatedly tested. The frequency of occurrence of covert saccades and the latency of the first covert saccade of a trace were analysed.

2.4.1. Extracting data

To extract saccades, head and eye velocity (Interacoustics and Otometrics) and position (Synapsys) traces were exported and processed using Wolfram Mathematica 11.3 (Wolfram Research, Champaign, IL, USA). Only traces that were accepted by the systems were exported.

2.4.2. Pre-processing data

Synapsys measures both eyes during VHIT, but in this study it was chosen to only use traces from the right eye, to better facilitate comparison with Interacoustics and Otometrics, which only register data from the right eye. In case of missing values from the right eye, data from the left eye was used. Because of the lower resolution of the Synapsys camera (100Hz), the original eye and head position data were resampled to 250Hz using linear interpolation. By differentiating these eye and head position traces, the velocity traces were calculated for eye and head movements recorded with the Synapsys system. Eye and head velocity traces from Interacoustics and Otometrics were directly extracted from the system itself. Eye and head position data for these two systems were calculated using numerical integration. Head and eye acceleration data were calculated for all three systems by differentiating the eye and head velocity signals.

2.4.3. Cleaning data

To establish artefact free traces for analysis, traces were removed when 1) peak head velocity was <120°/s, or 2) the head velocity trace contained a bounce at the end of the impulse of >50% of peak head velocity, or 3) head velocity never crossed zero after peak head velocity (within the recorded time frame), or 4) the head velocity trace contained missing values, or 5) the shape of the head velocity trace implied an inadequate head impulse, assessed by visual inspection and consensus between three authors (RB, DS, TD), or 6) when the mean head velocity of the interval of 80 ms prior and 120 ms after a peak head velocity was not in the range of ±3SD of the set of mean head velocities calculated in the same interval in all traces of one patient. [4, 15, 16]

2.4.4. Saccade detection

A custom-made algorithm was developed in Mathematica and applied to extract saccades from the eye traces. To increase accuracy, every saccade was verified by visual inspection of the eye and head velocity and position traces. Two authors needed to achieve consensus (TD, DS) before a saccade was approved. Head impulse onset was specified as head velocity exceeding 10°/s, head impulse offset was defined as head velocity crossing 0°/s. The onset of a saccade was marked as the point where eye velocity crossed 0°/s or eye acceleration reached 2000°/s^2. Saccades were included when 1) they occurred after peak head velocity, and 2) had a magnitude of more than 60°/s, and 3) peak velocity of the saccade was recorded, and 4) occurred at least in two traces around the same location within the same trial and patient. A saccade was classified as covert when onset occurred before head velocity crossed zero, and as overt when onset occurred after head velocity crossed zero.

2.4.5. Saccade analysis: defining frequency and latency

In this study, the first covert saccades of the first seven artefact-free traces were used for analysis. [17] The frequency and latency of the covert saccades were extracted from the original eye velocities in the Interacoustics and Otometrics system, and the calculated eye velocities in the Synapsys system. The frequency of occurrence of a covert saccade was first registered as a binary outcome (Yes/No) for every trace separately. From these data, a ratio per patient was calculated (in percentage). Latency (in milliseconds) was registered as the onset of the covert saccade and was normalised to the start of the head impulse. [18]

2.5. Statistical analysis

Data were analysed using SPSS Statistics 24 for Windows and R (v.3.5.2.). The α-value was set at $p<0.05$. In the case of multiple comparisons, the Bonferroni correction was applied. When

no interaction was found between leftwards and rightwards head impulses, the direction of the impulse was removed from the statistical model and both sides were analysed together.

2.5.1. Statistical analysis of VOR gain and agreement of VHIT systems regarding BV diagnosis
A repeated-measures ANOVA was used to compare the mean VOR gain between the three systems. A VOR gain of <0.6 was classified as "bilateral vestibulopathy", and a VOR gain of ≥0.6 was classified as "no bilateral vestibulopathy". [8] In case the VHIT systems showed a discrepancy in classifying BV, it was classified as "no agreement".

2.5.2. Statistical analysis of VOR gain and repetitive testing (the order effect)
To evaluate the order effect, a repeated-measures ANOVA was used to compare the mean VOR gain between the first and the last executed VHIT trial (regardless of the VHIT system).

2.5.3. Statistical analysis of peak head velocity
Peak head velocities (extracted from the raw traces of the VHIT systems) of all traces of all patients were combined per VHIT system. Median peak head velocities were compared between VHIT systems using a Mann-Whitney U test. In patients with "no agreement" between systems, peak head velocities were analysed separately within the BV patient. Median peak head velocities of those particular trials were compared between VHIT systems using a Mann-Whitney U test.

2.5.4. Statistical analysis of saccades
The frequency of occurrence of covert saccades was compared between the first and the last executed VHIT trial (regardless of the VHIT system) using a generalized linear mixed-effects model. Additionally, the latency of the first covert saccade was compared between the first and the last executed VHIT trial (regardless of the VHIT system) with a paired T-test. Patients with missing values (no saccades) were not included in this last analysis.

3. Results

3.1. Patient characteristics

In total 46 BV patients were included: 23 males and 23 females. The mean age was 59 years old (standard deviation of 11 years). Definite and probable etiologies comprised: ototoxic effects of antibiotics (n=8) or chemotherapy (n=1), post-infectious due to Lyme disease (n=1), Hashimoto's thyroiditis (n=1), Herpes infection (n=1), meningitis (n=2), inherited e.g., by DFNA9 gene mutation (n=7), bilateral Menière's disease (n=3), autoimmune disease (n=1). In 21 patients, no etiology could be determined (idiopathic).

All three VHIT systems were able to capture the same type of eye movement responses to head impulses. This is illustrated in Figure 2, which presents the raw data of one BV patient (patient 21), selected as a representative sample of the whole study population. Further details of VHIT characteristics (VOR gain, peak head velocity, timing of saccades) of all tested patients, will be discussed below.

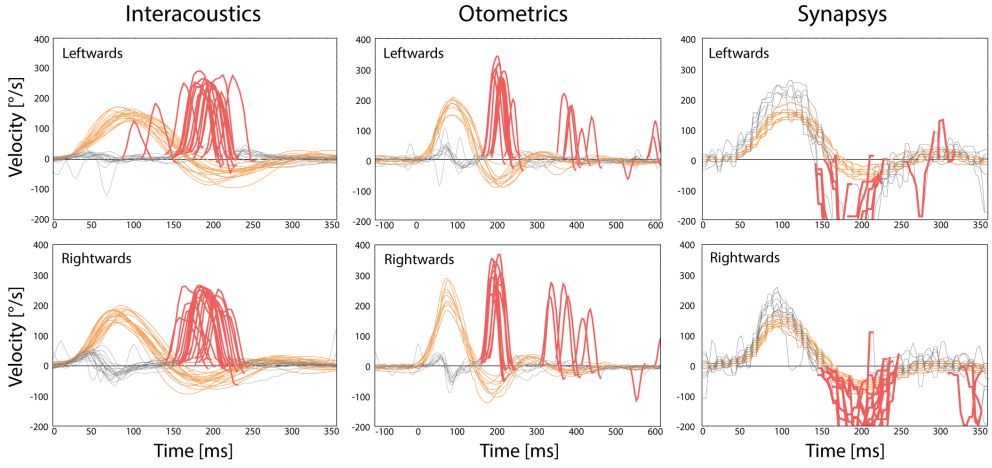

Figure 2. Raw eye and head movement data of one BV patient, obtained by three different VHIT systems during three consecutive VHIT trials. Grey dotted lines represent eye movements, orange lines represent head movements, and red lines represent saccades. Note that eye movements obtained with the Synapsys system have a different graphical representation. This is based on the fact that a space-fixed camera with a lower sampling rate was used, instead of a head-fixed camera.

3.2. VOR gain and agreement of VHIT systems regarding BV diagnosis

Figure 3 illustrates that different VOR gains were obtained by different VHIT systems, within the same BV patients. There was a statistically significant difference between the three systems in VOR gains ($F(1.256, 33.916)=35.681$, $p<0.000$). VOR gains obtained with the Synapsys system differed significantly from VOR gains obtained with the other two systems.

No statistically significant difference was found in VOR gains between the Interacoustics and Otometrics systems. Mean VOR gains of all patients were 0.33, 0.35, and 0.10 for Interacoustics, Otometrics, and Synapsys systems respectively.

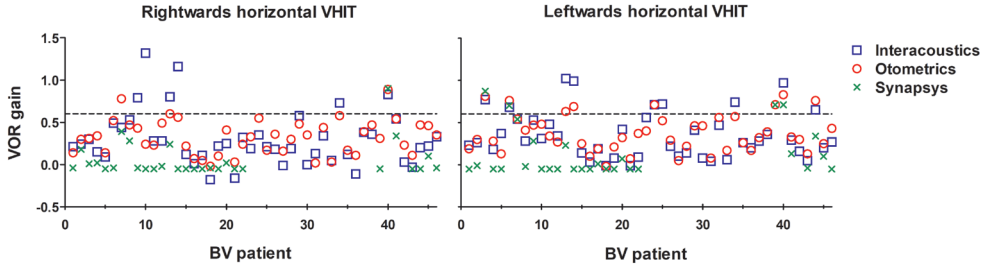

Figure 3. VOR gains for leftwards and rightwards horizontal VHIT, as tested with three different VHIT systems. Every symbol represents the VOR gain of one VHIT trial in one patient obtained with one VHIT system. The horizontal line at a VOR gain of 0.6 represents the cut-off value according to the BV criteria of the Bárány Society. [8] VOR gains obtained with the Synapsys system differed significantly from VOR gains obtained with the other two systems. No statistically significant difference was found in VOR gains between the Interacoustics and Otometrics systems.

The VHIT systems agreed in 83% of the 46 patients on the BV diagnosis ("bilateral vestibulopathy" or "no bilateral vestibulopathy") according to the criteria of the Bárány Society [8]. In eight patients (17%) no agreement was found (Table 1). These eight patients were diagnosed with BV resulting from various etiologies: ototoxic effects of gentamicin (n=1) and chemotherapy (n=1), bilateral Menière's disease (n=1), post-infectious due to Lyme's disease, (n=1) inherited (n=1), and idiopathic (n=3).

In the 28 patients tested with all three VHIT systems, the percentage of agreement between the VHIT systems was 79% (68% BV, 11% no BV), and in 21% there was no agreement. The mean VOR gains obtained in these 28 patients were 0.36, 0.36, and 0.09 for Interacoustics, Otometrics, and Synapsys respectively.

Table 1. Differences between VHIT systems, when diagnosing BV are only based on VOR gains. A horizontal VOR gain of <0.6 was classified as "bilateral vestibulopathy", and a VOR gain of ≥0.6 was classified as "no bilateral vestibulopathy". In case VHIT systems showed a discrepancy in the diagnosis of BV, the patient was classified as "no agreement". Not all patients were tested with all three systems since systems were not always available at the time of testing.

Diagnosis according to VHIT results	Interacoustics (N=45)	Otometrics (N=46)	Synapsys (N=28)	All patients (N=46)
Bilateral vestibulopathy	76%	80%	86%	72%
No bilateral vestibulopathy	24%	20%	14%	11%
No agreement between systems	16% Otometrics 24% Synapsys	16% Interacoustics 17% Synapsys	24% Interacoustics 17% Otometrics	17%

3.3. VOR gain and repetitive testing

No order effect was present, since no difference in VOR gain was found between the first and the last VHIT trial, regardless of the system used for VHIT.

3.4. Peak head velocity

For every VHIT system, median peak head velocities with their interquartile range of all traces together from all patients are presented in Table 2. A significant difference in the velocity of the head impulses between the three systems was found ($p<0.001$). Regarding the Synapsys system, significantly lower median peak head velocities (maximum 43°/s lower) and VOR gains (maximum 0.37 lower) were present than in the other two systems. Interacoustics and Otometrics did not significantly differ regarding VOR gain, only regarding median peak head velocity (maximum 11°/s).

Table 2. Median peak head velocities (with their first (Q1) and third quartile (Q3)) and median VOR gain (as calculated by the VHIT system) for rightwards and leftwards horizontal head impulses. There was a statistically significant difference in peak head velocities between the three systems. Both peak head velocity and VOR gain were lower in Synapsys than in the other two systems.

	Rightwards horizontal VHIT			Leftwards horizontal VHIT		
VHIT system	Peak head velocity	Q1 | Q3	VOR gain	Peak head velocity	Q1 | Q3	VOR gain
Interacoustics	207	183 | 229	0.22	198	175 | 217	0.28
Otometrics	215	192 | 240	0.32	209	186 | 231	0.33
Synapsys	178	156 | 200	-0.04	166	135 | 195	-0.04

Peak head velocities were separately analysed in the eight patients with “no agreement” on the diagnosis of BV according to the VHIT systems (Figure 3). In one out of eight patients, the median peak head velocity of the given head impulses was significantly higher in the system with the lower VOR gain. This patient showed in the Interacoustics system a VOR gain of 0.74 with a median peak head velocity of 196°/s (leftwards impulses) and a VOR gain of 0.73 with a median peak head velocity of 214°/s (rightwards impulses), versus a VOR gain of 0.57 with median peak head velocity of 265°/s (leftwards impulses) and a VOR gain of 0.58 with median peak head velocity of 255°/s (rightwards impulses) in the Otometrics system.

In the other seven patients, no statistically significant difference in peak head velocities between VHIT systems was found, or the system with significantly higher (or lower) peak head velocities also measured higher (or lower respectively) VOR gains in that patient. [19]

3.5. Frequency and latency of covert saccades

According to the strict methods described above, the frequency of covert saccades could be analysed in 34 patients, and the latency of covert saccades in 20 patients. In this study, no statistically significant difference in the frequency of occurrence of covert saccades and the latency of the first appearing covert saccade was found between the first and the last VHIT trial, regardless of the system (Figure 4).

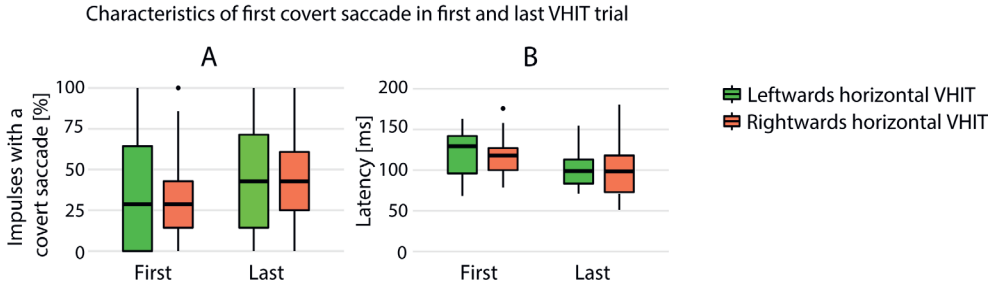

Figure 4. Characteristics of the first appearing covert saccade from the first seven artefact free traces of all patients together. **A.** The frequency of covert saccades (percentage of impulses with at least one covert saccade) in the first and last VHIT trial. **B.** Latency of the first covert saccade (the moment of onset of the saccade in milliseconds, start of head impulse is 0ms) in the first and last VHIT trial. No statistically significant difference was found in the characteristics between the first and the last VHIT trial regardless of the VHIT system (Interacoustics, Otometrics, or Synapsys).

4. Discussion

This study compared the VOR gains obtained with three commercially available VHIT systems (Interacoustics, Otometrics, and Synapsys) in a large group of BV patients. In 83% of the patients, the VHIT systems agreed on the diagnosis of BV, when using a cut-off horizontal VOR gain of <0.6. [8] Additionally, while VOR gains did not significantly differ between the Interacoustics and Otometrics systems, they both significantly differed from VOR gains obtained with the Synapsys system.

The fact that agreement between VHIT systems on BV diagnosis was present in 83% of the cases, implies that in 17% no agreement was present. This is suboptimal for diagnostic devices used in a clinical setting. It would be preferred to further investigate the origin of these differences in outcomes between VHIT systems, to improve the diagnostic pathway in BV patients. The origin might have (partially) resulted from inherent differences in the VHIT systems themselves, e.g., differences in eye and head tracking, and/or VOR gain calculation. This has been described before in healthy subjects, but this is the first study that shows the possible significant impact on the diagnosis of BV. [5, 6] It has been hypothesized that mainly the differences in the VOR gain calculation algorithm are responsible for the

VOR gain differences (*van der Lans, manuscript in preparation*). After all, especially in BV patients, the transfer function of the VOR is often not linear, and the appearance of covert saccades might interfere with VOR gain calculation. This implies that VOR gain outcomes are very sensitive to pre-processing (e.g., desaccading) and interpretation of the traces by the VOR gain calculation algorithm. To overcome some of these challenges, the Suppression Head Impulse Test (SHIMP) was proposed, which might decrease the number of covert saccades and better show the residual vestibular function [3, 13, 20] However, this paradigm still depends on the VOR gain calculation algorithm, and its clinical relevance in BV is yet to be determined (*van Dooren, manuscript in preparation*). Generally, it seems therefore necessary that VHIT systems are standardized regarding eye and head tracking methods and VOR gain calculation algorithms, to improve the proper diagnosis of BV. If this is not possible, it could be investigated whether VHIT system-specific cut-off values to diagnose BV are a possibility to increase agreement between VHIT systems. Nevertheless, it remains important to not only assess VOR gain, but also the raw traces and compensatory saccades. In addition, BV is diagnosed using a combination of symptoms and several vestibular tests (caloric test, rotatory chair test, VHIT). Since these vestibular tests are complementary, only performing VHIT might not be enough to rule out BV. [8, 21]

In this BV population, outcomes of the Synapsys system differed significantly from the other two VHIT systems: Synapsys showed a lower VOR gain than Interacoustics and Otometrics (Figure 3). This could (partially) be explained by differences in gain calculation algorithms, different eye- and head tracking methods (Synapsys uses a space-fixed camera, the other two systems use a camera fixed to a pair of goggles), or differences in sampling frequency (Synapsys uses a lower sampling frequency of 100Hz, compared to 220Hz and 245Hz for Interacoustics and Otometrics respectively). Furthermore, during the visual inspection, the Synapsys system showed fewer smooth eye velocity traces, and more missing values than Interacoustics and Otometrics (Figure 2). However, when the Synapsys system considered a patient “no BV” (VOR gain ≥0.6) this was always in agreement with both of the other two systems. Nevertheless, the other way around (“BV” with Synapsys and “no BV” in the other two systems) also occurred. It is unknown whether this was a systematic mistake of the Synapsys system, or whether Synapsys was the only system that was able to best detect BV in the high-frequency range of this population. This question was beyond the scope of this article but could be addressed in the future.

When observing differences in VOR gains between different VHIT systems and VHIT trials, it is very important to first rule out measurement artefacts, like clinically relevant differences in peak head velocities, the order effect, and differences in frequency and latency of covert saccades that could influence the VOR gain calculations. [5, 16, 21] Regarding differences in peak head velocities, a higher peak head velocity might result in lower VOR. [19] However, in

contrast to these findings, the system with significantly lower median peak head velocities during VHIT trials (Synapsys), also showed the lowest VOR gains in this study. Therefore, it is very unlikely that differences in peak head velocity between Synapsys and the other VHIT systems might have caused most of the VOR gain differences between VHIT systems in this study. The statistically significant difference in median peak head velocities between VHIT trials of Interacoustics and Otometrics was only small (11°/s difference), and therefore probably not influenced the (not significant) VOR gain differences between the two systems. [19] Regarding the order effect and the frequency and latency of covert saccades, VOR gains, and covert saccades did not show differences in this BV population with repetitive testing. This is in agreement with previous studies on healthy subjects and patients with vestibular dysfunction. [7, 22] Therefore, it can be concluded that it is very unlikely that measurement artefacts like the order effect or covert saccades, could explain the significant differences in VOR gains found between the three VHIT systems in this study.

Limitations

In patients with low VOR gains, biphasic eye movement artefacts can occur at the beginning of head impulses, when using a head-mounted VHIT system (e.g., Figure 2, eye movements obtained during rightward impulses with Interacoustics and Otometrics system). This might lead to erroneous higher VOR gains, especially when using the instantaneous gain calculation method (Interacoustics) compared to the area under the curve gain calculation method (Otometrics). [13, 16] This type of artefact was not specifically addressed in this study. Since VOR gains obtained with the Interacoustics and Otometrics systems did not significantly differ in this study, the comparison of these two systems was most likely not compromised by this artefact. However, it cannot be ruled out that this artefact might (partially) explain some of the relatively lower VOR gains in the Synapsys system.

5. Conclusion

To conclude, using different VHIT systems in the same BV patient, can lead to clinically significant differences in VOR gain when using a cut-off value of 0.6. This might hinder the proper diagnosis of BV patients. It would therefore be preferred that VHIT systems are standardized regarding eye and head tracking methods, and VOR gain calculation algorithms. Until then, it is advised to not only consider the VOR gain when assessing a VHIT trial but to also look at the raw traces and the compensatory saccades.

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CHAPTER 4

Suppression Head Impulse test (SHIMP) versus Head Impulse test (HIMP) when diagnosing Bilateral Vestibulopathy

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Abstract

Objective: The Suppression Head Impulse (SHIMP) test was introduced as an alternative to the Head Impulse Paradigm (HIMP), to overcome challenges in VOR gain calculation due to interference of covert saccades. The objectives of this study were 1) to determine if SHIMP, compared to HIMP, reduces covert saccades in BV patients, and 2) to define the agreement on diagnosing BV between SHIMP and HIMP.

Methods: First, it was determined whether covert saccades were eliminated during SHIMP, by comparing the number of covert saccades between SHIMP and HIMP. A custom-made algorithm detected saccades, after strict trace evaluation to exclude artefacts. Since the definition of covert saccades can be different between clinics, the latency of the first saccade (covert and/or overt) was analysed separately. Secondly, VOR gain was compared between SHIMP and HIMP. Lastly, the agreement between SHIMP and HIMP on identifying BV according to the diagnostic criteria (horizontal VOR gain <0.6) was evaluated. For this last analysis, the unfiltered data from the device were used, as will be the case in daily practice.

Results: A total of 98 BV patients was included. This study demonstrated fewer covert saccades, longer latencies of the first saccade, and a lower VOR gain for BV patients in SHIMP, compared to HIMP. These differences were statistically significant ($p<0.001$). In 93% of the patients, an agreement was found between the paradigms regarding the diagnosis of BV.

Conclusion: To our knowledge, this is the largest study population on SHIMP testing in BV patients. Covert saccades and VOR gains were significantly reduced during SHIMP, compared to HIMP. However, the clinical relevance of these statistically significant differences is small and both paradigms detect BV in the vast majority of patients. The Suppression Head Impulse (SHIMP) test was introduced as an alternative to the Head Impulse Paradigm (HIMP), to overcome challenges in VOR gain calculation due to interference of covert saccades. The objectives of this study were 1) to determine if SHIMP, compared to HIMP, reduces covert saccades in BV patients, and 2) to define the agreement on diagnosing BV between SHIMP and HIMP. First, the number of covert saccades was compared between SHIMP and HIMP. Secondly, VOR gain was compared between SHIMP and HIMP. Lastly, the agreement between SHIMP and HIMP on identifying BV (horizontal VOR gain <0.6) was evaluated. A total of 98 BV patients was included. To our knowledge, this is the largest study population on SHIMP testing in BV patients. Covert saccades were significantly reduced, and a lower VOR gain was found during SHIMP, compared to HIMP ($p<0.001$). However, the clinical relevance of these statistically significant differences is small. In 93% of the patients, an agreement was found between the two paradigms regarding the diagnosis of BV, and both paradigms detect BV in the vast majority of patients.

1. Introduction

The Head Impulse test (HIMP) is widely used to assess the vestibulo-ocular reflex (VOR) function of all semicircular canals in the high-frequency domain. During this test, the examiner performs fast head impulses (>120°/s) passive head movements with a small amplitude (10-30°), unpredictable in timing and direction. Subjects are asked to fixate on an earth-fixed target at eye level in front of them. In the case of a normal VOR, the eyes will immediately move in the contralateral direction of the head impulse, to assure gaze stability on the target. In patients with a deficient VOR, the eyes will move slower than the head, or even initially move along with the head. To correct for the loss of gaze, a compensatory eye movement (saccade) is required to refixate on the target. The appearance of these saccades indicates vestibular hypofunction. These saccades can appear after (i.e., overt saccade) or during (i.e., covert saccade) the head impulse. Overt saccades are often detected by the naked eye of the examiner. In contrast, this is mostly impossible for covert saccades. [1]

The HIMP can also be performed using a device that allows quantification of the VOR and detection of (overt and covert) saccades: the video head impulse test (VHIT). This device tracks head and eye movements during the head impulse test. Different types of devices are commercially available, including systems with head-mounted lightweight goggles or an earth-fixed remote camera. The main outcome parameter is VOR gain, calculated as the ratio between eye and head movement. VOR gain will be close to one in healthy subjects and lower in patients with a deficient VOR. [2] For example, a bilateral horizontal VOR gain of <0.6 is one of the main criteria for the diagnosis of bilateral vestibulopathy (BV). [3] Different algorithms can be used to calculate VOR gain. Covert saccades might challenge VOR gain calculation due to their interference with eye movements produced by the VOR. [4] This implies that VOR gain might not always perfectly reflect the VOR function. Current HIMP systems tend to overcome this issue by, for example, desaccading eye movements. [5]

In 2016 the Suppression Head Impulse test (SHIMP) was introduced by MacDougall et al. as an alternative to HIMP, to overcome challenges in VOR gain calculation due to interference of covert saccades. [6] The main difference between SHIMP and HIMP is a head-fixed target instead of an earth-fixed. The target is a laser dot projected by lightweight goggles. As a result, the target moves along with the head during the head impulse. In case of an adequate VOR, the eyes will initially move in the contralateral direction of the head. However, since the head-fixed target has moved during the impulse, these subjects need compensatory eye movements (saccades) to bring the eyes back on the target. Consequently, saccades during SHIMP represent (residual) vestibular function, while saccades during HIMP indicate a vestibular loss. [6] Moreover, saccades in SHIMP testing will mainly occur after the head impulse (overt saccades), and not during the head impulse (covert saccades). [1] Hence,

this elimination of covert saccades during SHIMP might facilitate a more precise VOR gain calculation than in HIMP.

Previous research demonstrated that SHIMP is a feasible test in healthy subjects and vestibular patients. In SHIMP a lower VOR gain was found, compared to HIMP. The underlying mechanism is not fully known, but several explanatory theories have been opted: less interference of covert saccades as described above (no desaccading of the traces necessary), or the influence of compensatory mechanisms that are possible during SHIMP (e.g., VOR cancellation/inhibition resulting in slower eye velocities). [6-8] The presence of covert saccades is lower in SHIMP than in HIMP. [6] However, the clinical consequence of eliminating covert saccades when using SHIMP has not yet been determined comprehensively in a large group of BV patients.

Therefore, the objectives of this study were 1) to determine if SHIMP, compared to HIMP, reduces covert saccades in BV patients, and 2) to define the agreement on diagnosing BV between SHIMP and HIMP. It was hypothesized that BV patients demonstrated fewer covert saccades and a lower VOR gain when tested with SHIMP compared to HIMP, but that these effects might not influence the diagnosis of BV in most patients.

2. Methods

2.1. Study population

This study comprised patients diagnosed with BV at the Division of Balance Disorders at Maastricht University Hospital in the Netherlands and Antwerp University Hospital in Belgium, based on the diagnostic criteria for BV from the Bárány Society. [3] Inclusion criteria comprised 1) reduced caloric response (sum of bithermal maximum peak slow phase eye velocities of <6 °/s on each side), 2) and/or reduced horizontal angular VOR gain <0.1 on rotatory chair and a phase lead >68°, 3) and/or bilateral horizontal VOR gain <0.6, measured by the VHIT. Exclusion criteria comprised being unable to stop vestibular suppressants for one week (cinnarizine and all psychiatric medication), and the inability to undergo one of the vestibular examinations.

2.2. Study design

A systematic approach was used. First, it was determined whether covert saccades were eliminated during SHIMP, by comparing the number of covert saccades between SHIMP and HIMP. A custom-made algorithm detected saccades, after strict trace evaluation to exclude artefacts as described in paragraph 2.3). Since the definition of covert saccades can

be different between clinics, the latency of the first saccade (covert and/or overt) was also analysed separately. Secondly, the VOR gain was compared between SHIMP and HIMP, and the influence of peak head velocity was determined. Lastly, the agreement between SHIMP and HIMP on identifying BV according to the diagnostic criteria (horizontal VOR gain <0.6) was evaluated. For this last analysis, the unfiltered data from the device were used, as will be the case in daily practice.

2.3. Experimental setup

To reduce the artefacts to a minimum, two trained examiners (FL, BD) followed a strict experimental setup, as described in previous articles. [9, 10] Every patient underwent testing in the same order (first HIMP, then SHIMP). All tests were performed using the ICS Impulse system (Natus, California, USA). Distance to the target, and room illumination were similar for all patients. [11] The right eye was tested in both SHIMP and HIMP paradigms. After calibration, the examiner nor the patient were allowed to touch the strap and the goggles. Patients were constantly kept alert by the instructions of the examiner. Fast (>120°/s), outwards, horizontal head impulses with a small amplitude (10-30°) were given, unpredictable in timing and direction. [12, 13]

2.4. Saccades

2.4.1. Saccade detection [14]

In order to determine saccades, first head and eye velocity traces were exported from the Otometrics system, and position and acceleration data were calculated using Wolfram Mathematica 11.3 (Wolfram Research, Champaign, IL, USA). Only traces that were accepted by the Otometrics system itself were exported. All traces were checked on artefacts. Traces were excluded from analyses when 1) peak head velocity was <120°/s, or 2) the head velocity trace had a bounce >50% of peak head velocity after the head impulse, or 3) head velocity never crossed zero after peak head velocity, or 4) the head velocity trace contained missing values, or 5) the head velocity trace differed from the standard shape, assessed by visual inspection and consensus between three authors (RB, DS, TD), or 6) when the mean head velocity of the interval of 80ms prior and 120ms after a peak head velocity was not in the range of ±3SD of the set of mean head velocities calculated in the same interval in all traces of one patient. [15]

A custom-made algorithm was applied to extract saccades from the eye acceleration traces, yet every saccade was verified by visual inspection of the velocity and position traces. Two authors needed to achieve consensus (TD, DS) before a saccade was approved. Saccades were included when they 1) occurred after peak head velocity, and 2) had a magnitude of

more than 60°/s, and 3) the peak saccade velocity was recorded. The onset of a saccade was the point where eye velocity crossed zero or eye acceleration reached 2000°/s^2. The offset of a saccade was the point where eye acceleration crossed zero after eye velocity crossed zero, or acceleration was below 2000°/s^2 when velocity did not cross zero. A saccade was classified as "covert saccade" when onset occurred before head velocity crossed zero, and as "overt saccade" when onset occurred after head velocity crossed zero. Head impulse onset was set on head velocity exceeding 10°/s. Head impulse offset was defined as head velocity crossing zero (Figure 1).

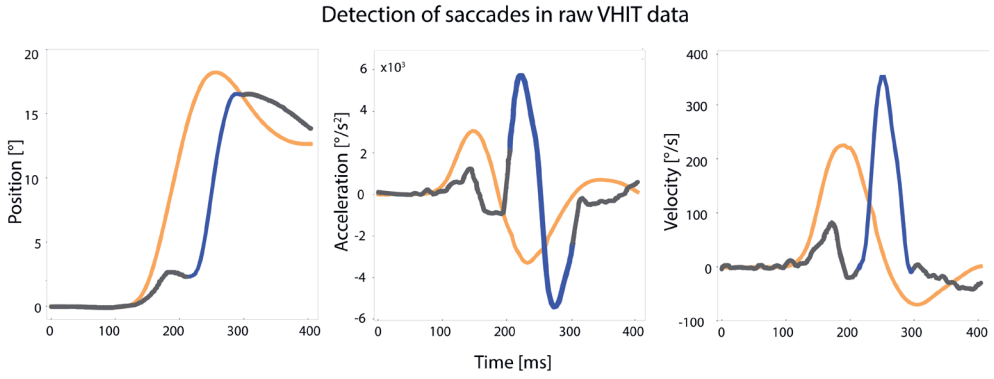

Figure 1. Detection of saccades in VHIT traces based on position, acceleration, and velocity of eye movement. The orange line illustrates the head impulse, the grey line represents the eye movement, and the blue line represents the saccade as included in the analysis. Raw data were exported from the Otometrics system (head and eye velocity traces). Position and acceleration data were calculated from these data. All traces were checked on artefacts and excluded if necessary. Saccades were extracted from these artefact-free traces, using a custom-made algorithm. All saccades were verified by visual inspection. Definitions of artefacts and saccades are described in paragraph 2.4.

2.4.2. Presence of covert saccades

The presence of covert saccades for every patient was determined as the frequency of occurrence of at least one covert saccade per trial. Every trial consisted of seven artefact-free traces (as described above). [16] Only the first saccade of a trace was used for analysis. As a result, every patient had a minimum of zero and a maximum of seven covert saccades per trial. The frequency of occurrence of a covert saccade was first registered as a binary outcome (yes/no) for every trace separately. From these data, a ratio (0-1) and percentage (0-100%) per patient were calculated.

2.4.3. Latency of saccades

The latency of the first saccades was extracted from the original eye velocities in the Otometrics system. Both overt and covert saccades were included. Latency (in milliseconds) was registered as the onset of the saccade and was normalised to the start of the head impulse.

2.5. VOR gain

For both HIMP and SHIMP, VOR gain was calculated by the Otometrics system itself over all traces accepted by the system. VOR gain was also calculated with a custom-made algorithm, using the raw data extracted from the Otometrics system. This VOR gain was calculated over the first seven artefact-free traces of every patient. Both methods (Otometrics system and custom-made algorithm) calculated the VOR gain by the ratio of the area under the curve of eye movement and head movement. The eye movement was desaccaded if needed. [5] In order to detect influences of head velocity on VOR gain outcomes in this study, peak head velocities were compared between HIMP and SHIMP.

2.6. Statistical analysis

Data were analysed using SPSS Statistics 25 for Windows and R (v.3.5.2.). The α-value was set at $p<0.05$.

2.6.1. Statistical analysis of saccades

2.6.1.1. Covert saccades

Marginal multilevel model analysis was applied with side (right/left), and test (HIMP/SHIMP) as independent variables and an unstructured covariance matrix of the residuals to detect a statistically significant difference in the frequency of covert saccades (ratio 0-1) in BV patients between HIMP and SHIMP testing.

2.6.1.2. Latency of first saccade (covert and/or overt)

A two-sided paired t-test was used to compare the latency (ms) of the first saccade between HIMP and SHIMP. This analysis included the first saccade (i.e., both covert and overt saccades) of the first seven artefact-free traces in every patient. Logically, patients without a saccade in HIMP or SHIMP were not included in this part of the analysis.

2.6.2. Statistical analysis of VOR gain

Marginal multilevel linear regression with side (right/left), VOR gain, and test (HIMP/SHIMP) as independent variables and an unstructured covariance matrix of the residuals were performed to detect a statistically significant difference in VOR gain in BV patients between HIMP and SHIMP testing. VOR gain as calculated by a custom-made algorithm over the first seven artefact-free impulses, was used for analysis.

2.6.3. Statistical analysis of peak head velocity

The difference in peak head velocities between HIMP and SHIMP was calculated with a two-sided paired t-test. Median peak head velocities (extracted from the raw traces of the VHIT system) of the traces used to calculate VOR gain, were used for analysis.

2.6.4. Analysis of agreement between HIMP and SHIMP regarding BV diagnosis

For this analysis patients were excluded if diagnosed with BV solely based on VHIT outcomes since VOR gain obtained by the VHIT was used as the outcome parameter. VOR gain calculated by the Otometrics system (using all accepted traces) was used, as will be the case in daily practice. A HIMP VOR gain of <0.6 was classified as "bilateral vestibulopathy", and a VOR gain of ≥0.6 was classified as "no bilateral vestibulopathy". [3] For SHIMP, two different cut-off values (<0.6 and <0.5) were used and separately analysed. In case the paradigms (HIMP and SHIMP) showed a discrepancy in classifying BV, the patient was classified as "no agreement". In patients with "no agreement", visual inspection and descriptive analysis by two authors (TD, RB) were performed. This comprised inspecting the presence and timing of covert saccades, comparing VOR gain calculated by the system and the custom-made algorithm, and assessing if the traces showed characteristics of BV.

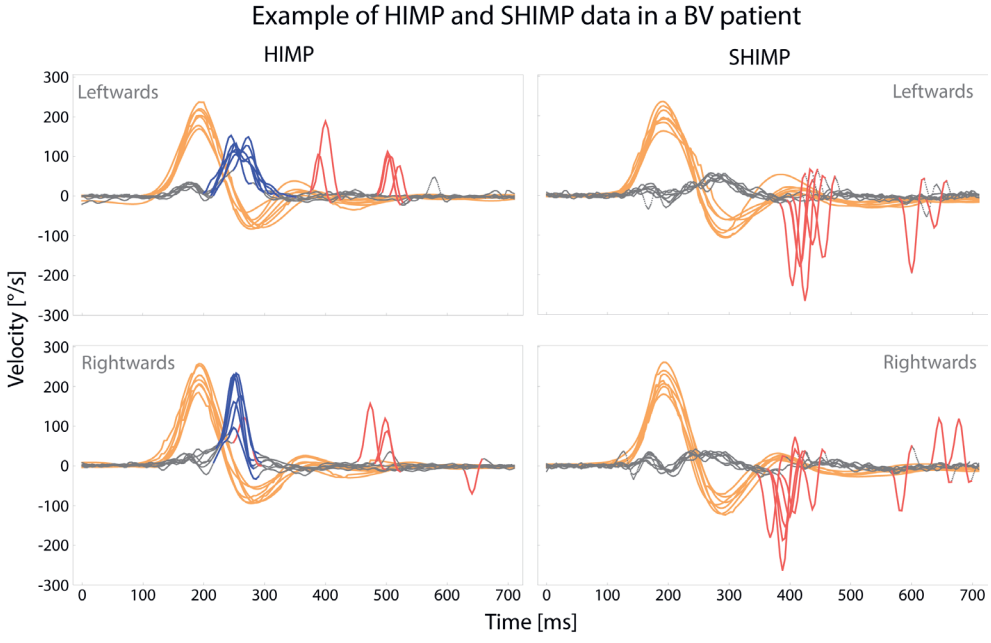

Figure 2. Raw eye and head movement data of one BV patient, obtained by HIMP and SHIMP during two consecutive VHIT trials. Grey lines represent eye movements, orange lines represent head movements, blue lines represent covert saccades, and red lines represent overt saccades.

3. Results

3.1. Patient characteristics

The study population comprised 98 BV patients from the Netherlands and Belgium: 56 males and 42 females. The mean age was 59 years old (SD 13 years). Definite and probable etiologies included: ototoxic effects of antibiotics (n=12) or chemotherapy (n=2); post-infectious due to Lyme disease (n=2), cerebral Malaria infection (=1), Herpes infection (n=1), meningitis (n=6), or neuritis (n=4); head trauma (n=5); inherited by DFNA9 gene mutation (n=13) or other gene mutations (n=10); bilateral Menière's disease (n=6); autoimmune disease (n=2). In 34 patients, no etiology could be determined (idiopathic).

A representative sample of an eye and head movements obtained with HIMP and SHIMP is illustrated in Figure 2. Further details of VHIT characteristics (saccades, VOR gain, and peak head velocity) of all tested patients will be discussed below.

3.2. HIMP versus SHIMP: the presence of covert saccades

A statistically significant difference was found in the presence of covert saccades between SHIMP and HIMP ($F(1,97)=86.314$, $p<0.001$). During SHIMP testing, fewer covert saccades were produced, compared to HIMP (estimated difference SHIMP-HIMP = -0.289 (-0.351, -0.227)). A covert saccade was present in 34-35% of the HIMP traces and 5-6% of the SHIMP traces (Figure 3A).

3.3. HIMP versus SHIMP: Latency of the first saccade (covert and/or overt)

This analysis comprised 92 patients for leftwards impulses and 93 patients for rightwards impulses, since patients without a saccade in HIMP or SHIMP could not be included. A statistically significant difference was found in the latency of the first saccade between SHIMP and HIMP ($p<0.001$). Saccades appeared later (i.e., demonstrated a longer latency) during SHIMP testing. The mean latency of the first saccade was 276ms on the left side and 274ms on the right side during SHIMP and 193ms for leftwards head impulses and 197ms for rightwards head impulses during HIMP (Figure 3B).

3.4. HIMP versus SHIMP: VOR gain differences

Mean VOR gain in SHIMP was lower, compared to HIMP (estimated difference SHIMP-HIMP = -0.026 (-0.040, -0.012). This difference was statistically significant ($F(1,97) =12.913$, $p<0.001$). Mean VOR gains for rightward and leftwards head impulses were respectively 0.32 and 0.33 in SHIMP, and 0.35 and 0.35 in HIMP (Figure 3C).

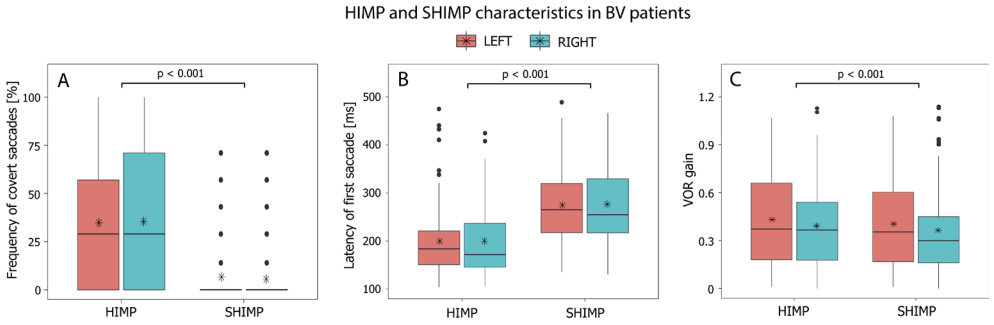

Figure 3. Characteristics of HIMP and SHIMP testing in BV patients for rightwards and leftwards head impulses: frequency of covert saccades (**A**), the latency of first saccade (covert and/or overt), (**B**), and VOR gain as calculated by a custom-made algorithm (**C**). Black horizontal lines represent median values, asterisks represent mean values for all patients.

3.5. HIMP versus SHIMP: peak head velocity

Median peak head velocity was significantly lower during SHIMP compared to HIMP ($p<0.001$) (Figure S1, Supplementary Material).

3.6. Analysis of agreement between HIMP and SHIMP regarding BV diagnosis

Six patients were excluded from this analysis since diagnosis of BV was solely based on VHIT outcomes, as described in paragraph 2.6.4. In 93% of the 92 patients HIMP and SHIMP agreed on the diagnosis of BV (either "bilateral vestibulopathy" or "no bilateral vestibulopathy"), when using the cut-off value of 0.6 for both paradigms (Table 1). In six patients (7%) the two paradigms did not agree on the diagnosis of BV. All these six patients were classified as "BV" with SHIMP, and "no BV" with HIMP. However, in three out of these six patients, HIMP and SHIMP agreed when using the VOR gain calculated by the custom-made algorithm. In the other three patients with no agreement, visual inspection did show a pathological eye-responses, but this was not reflected by a VOR gain <0.6. In case a SHIMP cut-off value of <0.5 was used, agreement on the diagnosis of BV increased to 97% (Table 1).

Table 1. Diagnosis of BV using HIMP and SHIMP (1a), and the agreement between both paradigms (1b) in 92 patients

1a. Diagnosis according to VHIT results	HIMP (cut-off <0.6)	SHIMP (cut-off <0.6)	SHIMP (cut-off <0.5)
Bilateral vestibulopathy			
VOR gain <0.6 on both sides	64	70	65
No bilateral vestibulopathy			
VOR gain >0.6 on both sides	10	9	14
VOR gain >0.6 on one side	18	13	13
1b. Agreement on the diagnosis of BV between HIMP and SHIMP			
HIMP (cut-off <0.6) and SHIMP (cut-off <0.6)		93%	
HIMP (cut-off <0.6) and SHIMP (cut-off <0.5)		97%	

4. Discussion

This study compared the outcomes of SHIMP and HIMP in a large group of 98 patients with Bilateral Vestibulopathy (BV), diagnosed according to the diagnostic criteria of the Bárány Society. [3] To our knowledge, this is the first study to compare SHIMP and HIMP in a patient population of this size.

SHIMP significantly reduced the number of covert saccades and VOR gain, compared to HIMP. More importantly, in 93% of the patients an agreement was found on the BV diagnosis between the two paradigms.

HIMP versus SHIMP: covert saccades

Significantly fewer covert saccades were produced by BV patients tested with SHIMP, compared to HIMP (0.05% vs. 35%) (Figure 3). This "covert saccade killer" phenomenon is in agreement with previous studies on smaller populations of patients with a vestibular deficit. [6, 7, 17] Elimination of covert saccades should facilitate a more accurate gain calculation. [6] This is especially valuable in a BV population, in which patients often produce covert saccades. [4]

HIMP versus SHIMP: VOR gain

VOR gain in SHIMP was significantly lower than in HIMP. However, the clinical implication of the VOR gain difference is small: only a mean difference of 0.02 (leftwards impulses) and 0.03 (rightwards impulses) (Figure 3). This VOR gain difference between both paradigms is slightly smaller, but comparable, to previous results in smaller groups of healthy subjects and BV patients. [6, 7] The underlying mechanism of a lower VOR gain in SHIMP is not fully known, but several explanatory theories have been opted. For example, the reduction of covert saccades could provide a more precise VOR gain calculation in SHIMP. However, a VOR gain difference (larger than in this BV population) between theses paradigms was also demonstrated in studies with healthy subjects (without covert saccades in HIMP testing). [7, 18] This might be explained by VOR response suppression, in which subjects decrease their VOR response. VOR suppression in unexpected passive movements is observed within 60-90ms after start of head movement, and therefore could be reflected in a lower VOR gain during SHIMP testing. [8, 19] Furthermore, higher head velocities result in lower VOR gains. [20] In this study, peak head velocities were significantly lower during SHIMP testing, which could therefore not justify the lower VOR gains in SHIMP.

HIMP versus SHIMP: agreement on the diagnosis of BV

Agreement between HIMP and SHIMP on the diagnosis of BV (VOR gain <0.6) was found in 93% of this population (Table 1). This suggests that the significant differences observed

between both paradigms (presence of covert saccades and VOR gain) probably have minor clinical consequences, since both paradigms detect BV in the vast majority of the patients.

The six patients in which HIMP and SHIMP did not agree on the BV diagnosis (when using a SHIMP cut-off value of <0.6), were all diagnosed as BV by SHIMP, and not with HIMP. These discrepancies could be attributed to gain calculation and cut-off values. Regarding gain calculation, a custom-made algorithm and visual inspection of the traces, did show severe vestibular hypofunction in these cases in both paradigms. Although, it must be stressed that also with the custom-made algorithm no agreement was found between both paradigms in 5 out of 92 patients. This demonstrates the need for a standardized approach to evaluate and interpret head impulse testing outcomes. This should include a universal gain calculation algorithm combined with assessment of the raw traces. [4, 21] Regarding cut-off values, two cut-off values were used for SHIMP in this study (VOR gain <0.6 and <0.5). Although no official cut-off values have been published for SHIMP, it was previously proposed to state a lower cut off value, considering the lower VOR gain values during SHIMP. [22] In this study, lowering the SHIMP cut-off value to 0.5 increased the agreement between HIMP and SHIMP to 97%. However, an increase in agreement does not imply an increase in the correctly made BV diagnoses. After all, less patients were diagnosed with BV after lowering the cut-off value to 0.5, while BV was already demonstrated by caloric testing and/or rotatory chair testing. This implies that future research is needed to determine the proper cut-off value for SHIMP in BV.

HIMP versus SHIMP: the daily practice

Both HIMP and SHIMP were well tolerated by all patients, and some of them reported that SHIMP testing felt more like a game than a medical test. Unfortunately, the current clinically available SHIMP software does not include testing of vertical semicircular canals. Therefore, when testing of all six semicircular canals is needed (e.g., in research setting, like vestibular implant research), HIMP testing is preferred. [23] Nevertheless, since SHIMP demonstrated to be a “covert saccade killer”, SHIMP could be an alternative in clinical settings which do not have the financial means to obtain a VHIT system. A less expensive diagnostic headband could be used during head impulses, while the examiner observes the presence or absence of overt saccades. [24]

Limitations

Testing was not randomized. SHIMP was always tested after HIMP, since these tests were part of a whole testing day. However, if more coverts were produced during the second test (SHIMP) due to a learning effect, it would only underestimate the significant decrease of covert saccades in SHIMP. Moreover, previous studies with BV patients and healthy subjects

showed no difference in covert saccades and/or VOR gain when tested repeatedly. [9, 14] Therefore, it can be expected that randomization would not have significantly influenced the study.

5. Conclusion

To our knowledge, this is the largest study population on SHIMP testing in BV patients. Covert saccades and VOR gains were significantly reduced during SHIMP, compared to HIMP. However, the clinical relevance of these statistically significant differences is small and both paradigms detect BV in the vast majority of patients.

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Supplementary Material

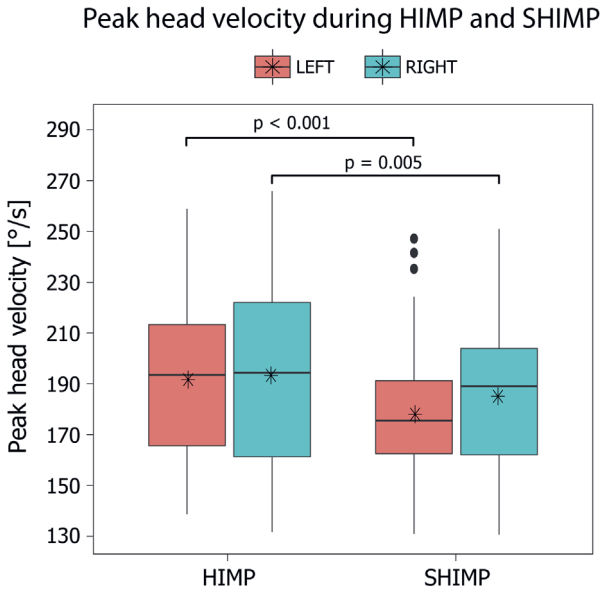

Figure S1. Peak head velocities during HIMP and SHIMP testing in 98 BV patients for rightwards and leftwards head impulses. Black horizontal lines represent median values, asterisks represent mean values for all patients. During SHIMP testing the peak head velocity was statistically significantly lower than during HIMP testing ($p<0.001$ and $p=0.005$ for leftwards and rightwards head impulses respectively).

CHAPTER 5

The functional Head Impulse Test (fHIT) to assess dynamic visual acuity and oscillopsia in patients with Bilateral Vestibulopathy

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Abstract

Introduction: Bilateral vestibulopathy (BV) is a chronic condition in which vestibular function is severely impaired or absent in both ears. Oscillopsia is one of the main symptoms of BV. Oscillopsia can be quantified objectively by functional vestibular tests, and subjectively by questionnaires. Recently, a new technique for visual stabilization abilities was developed: the functional head impulse test (fHIT). This study compared the fHIT with the Dynamic Visual Acuity assessed on a treadmill ($DVA_{treadmill}$) and Oscillopsia Severity Questionnaire (OSQ) in the context of objectifying dynamic visual acuity and the experience of oscillopsia in patients with BV.

Methods: Inclusion criteria comprised: 1) summated slow phase velocity of nystagmus of <20°/s during bithermal caloric tests, 2) torsion swing tests gain of <30% and/or phase <168°, and 3) complaints of oscillopsia and/or imbalance. During the fHIT (BEON Solutions SRL, Italy) patients were seated in front of a computer screen. During a passive horizontal head impulse, a Landolt C optotype was shortly displayed. Patients reported the seen optotype by pressing the corresponding button on a keyboard. The percentage of correct answers was registered for leftwards and rightwards head impulses separately. During $DVA_{treadmill}$ patients were positioned on a treadmill in front of a computer screen that showed Sloan optotypes. Patients were tested in static conditions and in dynamic conditions (while walking on the treadmill at 2, 4, and 6km/h). The decline in LogMAR between static and dynamic conditions was registered for each speed. Every patient completed the Oscillopsia Severity Questionnaire (OSQ), developed by the Division of Balance Disorders in Maastricht.

Results: In total 23 patients were included. This study showed a moderate correlation between OSQ outcomes and the fHIT (rightwards head rotations (r_s=-0.559; p=0.006) leftwards head rotations (r_s=-0.396; p=0.061)). No correlation was found between OSQ outcomes and $DVA_{treadmill}$, or between $DVA_{treadmill}$ and fHIT. All patients completed the fHIT, and 52% of the patients completed the $DVA_{treadmill}$ at all speeds.

Conclusion: The fHIT seems to be a feasible test to quantify oscillopsia in BV since, unlike $DVA_{treadmill}$, it correlates with the experienced oscillopsia measured by the OSQ, and more BV patients can complete the fHIT than $DVA_{treadmill}$.

1. Introduction

Gaze stabilization is one of the many functions of the vestibular system. The vestibulo-ocular reflex (VOR) enables gaze stabilization during high-frequency head movements by moving the eyes directly in the opposite direction of the head movement. A decreased VOR, therefore, impairs gaze stabilization, which leads to head or body movement-induced blurred vision (oscillopsia). Oscillopsia is one of the main symptoms of Bilateral Vestibulopathy (BV). [1]

BV is a heterogeneous chronic condition in which vestibular function is severely impaired or absent in both ears. [2] BV patients have a variety of symptoms and report a significant reduction in quality of life. Therapeutic options are often limited to balance training, but studies are now focusing on restoring vestibular function with a vestibular implant. [3-6]

To treat patients with BV, the condition must be first recognized by clinicians. The diagnosis of BV is often under or misdiagnosed. Therefore, sufficient inclusion criteria and validated patient-reported outcome measures are needed for patients with BV. One of the components is to quantify the experience of oscillopsia in BV patients. [2, 7]

Oscillopsia can be quantified subjectively by questionnaires, such as the Oscillopsia Severity Questionnaire (OSQ). [8] These questionnaires are designed to classify the disease burden experienced by patients in daily life. Additionally, oscillopsia can be quantified objectively by functional vestibular tests that assess dynamic visual acuity (DVA). [9, 10] Various clinical testing paradigms have been proposed to assess DVA, like walking on a treadmill or passively shaking the head, while reading an optotype chart. [8, 11] A new technique was recently suggested: the functional head impulse test (fHIT). The fHIT provides information about the functional performance of the rotational VOR by testing its gaze stabilization ability during passive head impulses in a range of peak head accelerations from 3000 to 6000 deg/s^2. [12-15]

The aim of this study was to compare the fHIT with the DVA on a treadmill ($DVA_{treadmill}$) and OSQ outcomes in the context of quantifying oscillopsia in BV patients. Preliminary data from our laboratory showed inter-and intrasubject discrepancies between fHIT and $DVA_{treadmill}$ results in patients with BV. This might be the result of the different stimuli applied during these tests: fHIT selectively stimulates the horizontal semicircular canals with passive head movements, while $DVA_{treadmill}$ stimulates the whole vestibular system with active whole-body movements. Based on these experiences, it was hypothesized that: 1) fHIT and $DVA_{treadmill}$ differ concerning quantifying oscillopsia since different stimuli are given, and 2) therefore one of them might correlate better to the OSQ.

2. Methods

2.1. Study population

This study comprised patients diagnosed with BV at the Division of Balance Disorders at Maastricht University Hospital. Inclusion criteria were: 1) summated slow phase velocity of nystagmus of <20°/s during biothermal caloric tests (30°C and 44°C, 300mL in 30 seconds), 2) Torsion swing tests gain of <30% and/or phase <168° (peak velocity of 60°/s; sinusoidal rotation 0.11Hz), and 3) complaints of oscillopsia and/or imbalance. The inclusion criteria differed in some aspects from the diagnostic criteria of BV from the Bárány Society since the inclusion of this study started before these criteria were published. [1] Based on normative data in our laboratory, the lower limit of a normal caloric test on one side is a sum of bithermal slow phase velocities of nystagmus of 25°/s (15°/s warm, 10°/s cold). BV patients included in this study had a maximum sum of bithermal slow phase velocities of nystagmus on one side of 15°/s. In this study, some patients will not perfectly fit the BV criteria from the Bárány Society, nonetheless, they definitely have a bilateral vestibular dysfunction (see Supplementary Material).

Exclusion criteria comprised peripheral neuropathy, being unable to stop vestibular suppressants for one week (cinnarizine and all psychiatric medication), or the inability to walk independently.

2.2. Testing

Every patient underwent fHIT and $DVA_{treadmill}$ on one day in the same order and with a break in between. Both tests were performed by one trained examiner (FL) under standardized conditions, in the same room with controlled illumination. Patients were tested binocularly and corrective spectacles or contact lenses were worn during fHIT and removed during $DVA_{treadmill}$.

2.2.1. Functional head impulse test (fHIT) [12-14]

The fHIT was performed using the fHIT system (Beon Solutions SRL, Zero Branco (TV), Italy). Patients were seated in a static chair in front of a computer screen at a distance of 1.5 meters with a keyboard in their hand. During a passive head impulse, when head acceleration reached its peak value, an optotype (Landolt C ring) was displayed on the screen for 80ms. The size of the optotype was adjusted for every subject separately and remained constant during testing. Before the start of the fHIT, the static visual acuity threshold was acquired by the fHIT system in 20 trials. Optotype size started from 1.0 LogMAR (log of the Minimum Angle of Resolution) and decreased depending on the subjects' rates of errors. The used optotype size was equal to this threshold, increased by 0.6 LogMAR. [13] During

fHIT, patients had to choose the right optotype out of eight different options by pressing the corresponding button on the keyboard. No direct feedback was given. Head impulses comprised fast (peak velocity >150°/s) [16, 17], outwards, passive, horizontal rotational head movements with low amplitude (+/-20°), unpredictable in timing and direction. At least 10 impulses were given to both sides. The absolute outcome was the percentage of correct answers (%CA) for each side, as calculated by the fHIT system. A %CA of less than 80 was considered abnormal. This cut-off was a conservative approximation of the criterion adopted by the fHIT system, which considers the level where the standardized normal deviation of the patient falls outside the 99% of the two-tailed Z distribution of a population of age-matched controls. [14]

2.2.2. $DVA_{treadmill}$

DVA was assessed on a treadmill (1210 model, SportsArt, Inc., Tainan, Taiwan, China) with a computer screen placed at a distance of 2.8 meters from the subject. Sloan letter optotypes were used. Testing started with optotypes presented at a LogMAR of 1.0. When 4 out of 5 optotypes were recognized correctly, the corresponding LogMAR was considered achieved and the size was decreased by steps of 0.1 LogMAR. When 3 or fewer optotypes were recognized correctly, the corresponding LogMAR was considered unachieved. The best (i.e., lowest) achieved LogMAR was recorded. Patients were tested in static conditions (while standing still) and in dynamic conditions (while walking on the treadmill at 2, 4, and 6km/h). Every condition was tested once. In case the patient was not able to walk independently at a certain speed, the test was stopped and registered as impossible for that speed. The absolute outcome for every speed was the visual acuity difference (VA difference), calculated as the decline in LogMAR between static and dynamic conditions. $DVA_{treadmill}$ was considered abnormal when a VA difference of >0.2 was recorded at 2 and 4 km/h or >0.3 at 6km/h. [8, 18, 19]

2.2.3. Oscillopsia Severity Questionnaire (OSQ)

Every patient completed the oscillopsia severity questionnaire (OSQ) developed by the Division of Balance Disorders in Maastricht. The OSQ consists of nine questions about the patients' experience of oscillopsia in daily life, as shown in Table 1. Every question can be answered by one of the following five options Always (=5), Often (=4), Sometimes (=3), Seldom (=2) or Never (=1). The outcome of every separate question was registered and the mean value for every patient was calculated. A mean value of 3 or more was considered as moderate to extreme oscillopsia severity. [8, 20]

Table 1. The Oscillopsia Severity Questionnaire (OSQ)

Oscillopsia Severity Questionnaire
1. Do you have the sensation that the visual environment is moving when it's not?
2. By dim light, do you have the sensation that the visual environment is not stable?
3. Is it difficult for you to recognize known faces when you are walking?
4. When you are reading, do you have the sensation that the text is not stable?
5. When you are watching television, do you have the sensation that the image is not stable?
6. When you are driving your car, do you have the sensation that the visual environment is not stable?
7. As a car passenger, do you have the sensation that the visual environment is not stable?
8. When you are riding a bicycle, do you have the sensation that the visual environment is not stable?
9. When you are walking on uneven ground, do you have the sensation that the visual environment is not stable?

Questions can be answered with Always=5, Often=4, Sometimes=3, Seldom=2 or Never=1. A mean value of 3 or more was considered as moderate to extreme oscillopsia severity.

2.3. Statistical analysis

Data were analyzed using SPSS Statistics 24 for Windows. Significance was set at $p<0.05$. Bonferroni correction was used in case of multiple comparisons. The Shapiro-Wilk test and visual inspection of the histogram and normal Q-Q plot of the outcome distributions were used to determine whether the data were normally distributed. In case there was no normal distribution of data, non-parametric tests (Wilcoxon Sign-Rank test, McNemar, Mann-Whitney U, or Spearman's Rank Correlation test) were used.

The correlation was calculated between fHIT and $DVA_{treadmill}$, between $DVA_{treadmill}$ (VA difference) at 2, 4, and 6km/h and OSQ score, and between fHIT (%CA) and OSQ score. Duration of illness was compared between DVA outcome and OSQ score, and between fHIT outcome and OSQ score.

During further analyses 3 groups were differentiated: (1) fHIT abnormal versus normal for rightwards and leftwards head rotations. In case fHIT was abnormal to at least one side, the outcome was considered abnormal during this analysis. (2) $DVA_{treadmill}$ impossible versus possible. The impossible subgroup consists of patients that were not able to walk independently at 2, 4, and/or 6km/h. (3) $DVA_{treadmill}$ abnormal versus normal. During this analysis patients with an impossible $DVA_{treadmill}$ at any speed were considered missing data. Within these groups, OSQ outcomes were compared between the subgroups.

2.4. Ethical considerations

This study was following the Declaration of Helsinki (amended version 2013). Approval was obtained from the ethical committees of Maastricht University Medical Centre (NL52768.068.15 / METC 151027). All participants provided written informed consent before the study.

3. Results

In this study, 23 patients with BV were included, 13 male and 10 female. The mean age was 57.6 (SD 11.04). The duration of illness varied between 18 months and 33 years. Etiologies comprised: ototoxicity due to gentamicin treatment (3) or chemotherapy (1), post-infectious due to Lyme disease (1) or meningitis (1), DFNA-9 gene mutation (3), bilateral Ménière's disease (2), autoimmune disease (1). In 10 patients, no cause could be found (idiopathic).

3.1. fHIT

All 23 patients (100%) completed the fHIT. Outcomes for rightwards and leftwards head rotations did not significantly differ. Eighteen patients (78%) showed an abnormal fHIT on both sides, and four patients (17%) had normal fHIT outcomes. One patient (4%) had a unilateral abnormal fHIT: 45 %CA on the right side and 90 %CA on the left side. No significant difference was found in OSQ scores between patients with normal and abnormal fHIT. A moderate correlation was found between %CA on the fHIT and OSQ score for rightwards (r_s=-0.559, p=0.006) and leftwards (r_s=-0.396, p=0.061) head impulses (Figure 1).

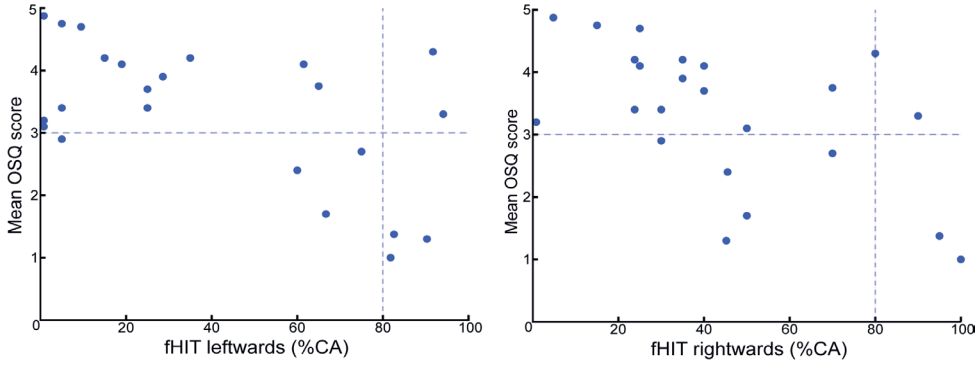

Figure 1. fHIT outcome (percentage of correct answers, %CA) versus mean OSQ score. The horizontal interceptive line represents the cut-off value of the OSQ; a value of 3 or more is considered as moderate to extreme oscillopsia severity. The vertical interceptive line represents the cut-off value of the fHIT; a %CA-value of less than 80 was considered abnormal. This study showed a moderate correlation between the severity of oscillopsia tested by the OSQ, and the percentage of correct answers on the fHIT for both rightwards (r_s=-0.559; p=0.006) and leftwards (r_s=-0.396; p=0.061) head impulses.

3.2. $DVA_{treadmill}$

In total 12 BV patients (52%) completed the DVA on all three speeds. With increasing speed, the number of patients that could not walk independently (and did not complete the test) increased: two patients at 2km/h and 11 patients at 6km/h. VA difference between 2, 4, and 6km/h did not differ statistically significantly. DVA, at any speed, was only abnormal in four patients (17%). All four patients showed abnormal DVA at 4km/h, and one even at 2km/h.

Of these four patients, neither completed a walking speed of 6km/h (Table 2). Mean OSQ outcome and duration of illness did not differ significantly between patients with a normal or abnormal DVA or between patients with a possible or impossible DVA. No correlation was found between OSQ outcome and the amount of VA difference at any speed.

Table 2. $DVA_{treadmill}$ outcomes. $DVA_{treadmill}$ was considered abnormal when a VA difference of >0.2 was recorded at 2 and 4km/h or >0.3 at 6km/h. In case a patient could not walk at a certain speed independently, this speed was classified as "not possible".

	DVA 2km/h	DVA 4km/h	DVA 6km/h	DVA all speeds *
Normal	20 (87%)	16 (70%)	12 (52%)	8 (35%)
Abnormal	1 (4%)	4 (17%)	0 (0%)	4 (17%)
Not possible	2 (9%)	3 (13%)	11 (48%)	11 (48%)

* DVA at all speeds was classified as "not possible" or "abnormal" when a patient did not complete the $DVA_{treadmill}$ protocol at all speeds or had an abnormal outcome at one or more speeds.

3.3. fHIT versus $DVA_{treadmill}$

fHIT showed more abnormal outcomes than $DVA_{treadmill}$ at all speeds: 78% versus 17%. Next to this, fHIT was possible in all 23 patients, while $DVA_{treadmill}$ could not be completed in 11 of them. All 4 patients with abnormal $DVA_{treadmill}$ outcomes, showed abnormal bilateral fHIT outcomes as well. No correlation between fHIT and $DVA_{treadmill}$ was found at any tested speed (2, 4, 6km/h), for both rightwards and leftwards head rotations.

4. Discussion

This study compared the fHIT with DVA assessed on a treadmill and OSQ outcomes in the context of quantifying oscillopsia in patients with BV. fHIT outcomes showed a moderate correlation with the experienced oscillopsia in daily life, as assessed by the OSQ. $DVA_{treadmill}$ outcomes, at any of the tested speeds, did not correlate to the severity of oscillopsia, as measured by OSQ. This is in agreement with previous studies with a large study population of BV patients. [8] There is no gold standard for measuring oscillopsia, this study used the Oscillopsia Severity Questionnaire (OSQ) to capture the subjective complaints of BV patients. [8] Specific questions from this questionnaire – those with the highest correlation with fHIT – could be of value in establishing validated patient-reported outcome measures for BV. [7]

fHIT showed more abnormal outcomes than $DVA_{treadmill}$ at all speeds (78% versus 17%). This is probably due to multiple factors. [9] First, the ability to compensate or adapt is less during fHIT than during $DVA_{treadmill}$. During walking on a treadmill, patients are able to use compensation mechanisms to improve gait or gaze stabilization (e.g., by trying to minimize

the overall head movement). Secondly, an active movement is made during $DVA_{treadmill}$, in contrast to the passive movement during fHIT. Passive movements have been shown to be most useful in discriminating between healthy subjects and patients with bilateral vestibular loss. [16, 21] Indeed, during walking an efference copy of the command producing the walking movement is available, thereby allowing patients to predict the retinal slippage as a consequence of the resulting head movement. [22] Thirdly, the nature of the stimulus differs between the two tests. The fHIT selectively stimulates the plane of one semi-circular canal during passive head movements in high frequencies (>150°/s), while $DVA_{treadmill}$ comprises an active movement that stimulates all semi-circular canals and otoliths at the same time. [14] The frequency of the stimulus depends on the walking speed. When walking at a speed of 6km/h, angular velocities are approximately 178°/s, and lateral and horizontal head translations occur at 1 Hz and 2 Hz respectively. [23]

BV criteria, and the inclusion criteria of this study, comprise a low or absent function of the horizontal semi-circular canal. In case the patient had a residual function of other sensory parts of the vestibular system (i.e., the otoliths), it could be possible that this residual function was used during $DVA_{treadmill}$. This possible selection bias could lead to false-negative $DVA_{treadmill}$ outcomes. These mechanisms might also (partially) explain why the fHIT has a stronger correlation to oscillopsia experience than $DVA_{treadmill}$.

Comparing the ability of subjects to complete a test, fHIT could be performed in more patients than $DVA_{treadmill}$. After all, in this study population, 100% of the patients were able to complete the fHIT, while 87% of the patients completed the DVA protocol at 4km/h and only 52% at 6km/h. The inability to walk faster than 5km/h on a treadmill in BV patients was described in previous studies. [11, 24]

A possible limitation of this study is the fact that $DVA_{treadmill}$ was tested without wearing any corrective spectacles. It is unlikely this has influenced the outcomes, since $DVA_{treadmill}$ outcome (VA difference) was calculated as the decline in LogMAR in a patient between static and dynamic conditions, both tested without corrective spectacles. Furthermore, different $DVA_{treadmill}$ cut-off values are reported in the literature. [1, 8, 18, 19] In this study, cut-off values were based on walking-speed-specific normative values from the vestibular laboratory in Maastricht. Despite the fact this study showed a moderate correlation between fHIT and OSQ, the correlation between objective and subjective tests to quantify oscillopsia is not (yet) optimal. It is possible that the used questionnaire (OSQ) captures more complaints than only oscillopsia and can be influenced by a patients' coping with BV. Lastly, in this article fHIT and $DVA_{treadmill}$ are compared. Both tests give different stimuli to the vestibular system, as described above, and are therefore never fully comparable.

To summarize, the fHIT seems feasible for quantifying oscillopsia in patients with BV. In the future, it possibly could also be used to measure functional outcomes in patients implanted with a Vestibular Implant.

5. Conclusion

The functional head impulse test (fHIT) is a recently proposed technique to assess visual gaze stabilization ability. The fHIT seems to be a feasible test to objectify oscillopsia in BV since, unlike DVA assessed on a treadmill, it correlates with the experienced oscillopsia measured by the OSQ, and more BV patients can complete the fHIT than DVA assessed on a treadmill.

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7. Appendix

				Calorics (slow phase velocity of nystagmus in °/s)					Torsion swing		VHIT	
	Etiology	Age	Sex	Warm right	Warm left	Cold left	Cold right	Sum	Gain (%)	Phase (°)	VOR gain left	VOR gain right
1	Idiopathic	53	M	0	0	0	0	0	1	-132	0.07	0.03
2	Gentamicin	74	V	6	0	0	0	6	41	159	0.46	0.48
3	Idiopathic	47	M	7	0	0	7	14	22	158	0.28	0.62
4	Gentamicin	79	M	0	0	0	0	0	2	28	0.46	0.35
5	Idiopathic	49	M	0	0	0	0	0	3	-159	0.08	0.02
6	Gentamicin	60	M	0	0	0	0	0	7	-197	0.56	0.44
7	DFNA-9	58	M	0	0	0	0	0	4	129	0.17	0.03
8	Menière's disease ADS	69	V	2	3	5	2	12	52	143	0.88	0.92
9	Idiopathic	36	M	8	0	0	7	15	18	-172	0.49	0.72
10	Lyme disease	42	M	7	1	0	2	10	7	-228	0.57	0.58
11	DFNA-9	62	M	0	0	0	0	0	2	24	0.26	0.17
12	Idiopathic	55	V	0	0	0	0	0	0	302	0.17	0.11
13	Idiopathic	49	V	0	0	0	0	0	10	-246	0.32	0.39
14	Auto-immune	65	M	0	0	0	0	0	5	209	0.39	0.47
15	Idiopathic	67	V	0	0	0	0	0	34	-222	0.71	0.31
16	Bacterial meningitis	55	V	0	10	3	0	13	12	146	0.34	0.29
17	Menière's disease ADS	75	V	9	0	0	0	9	8	129	0.83	0.89
18	Idiopathic	65	M	0	2	0	5	7	26	-242	0.33	0.54
19	Idiopathic	51	V	0	0	0	0	0	3	191	0.30	0.23
20	DFNA-9	56	V	0	0	0	0	0	3	6	0.13	0.11
21	Chemotherapy	46	M	0	0	0	0	0	28	154	0.76	0.47
22	Familial	64	V	0	0	0	0	0	12	-242	0.25	0.46
23	Idiopathic	60	M	0	3	0	0	3	2	98	0.43	0.35

Overview of the characteristics and measurements of the study population. Calorics was performed in both ears with a water temperature of 30°C and 44°C (300mL in 30 seconds). Inclusion criteria consisted of summated slow phase velocity of nystagmus of <20°/s during biothermal caloric tests. Based on normative data in our laboratory, the lower limit of a normal caloric test on one side is a sum of bithermal slow phase velocities of nystagmus of 25°/s (15°/s warm, 10°/s cold). The torsion swing test was performed with a peak velocity of 60°/s and a sinusoidal rotation of 0.11Hz. Inclusion comprised gain of <30% and/or phase <168°. The VHIT was performed with the ICS Impulse 3-D VHIT system (GN Otometrics, Denmark) and was not part of the inclusion criteria.

CHAPTER 6

General discussion and valorisation

General discussion and valorisation

The lifetime prevalence of a vestibular disorder is up to 10%. [1] Timely diagnosis and treatment of vestibular disorders considerably reduce health care costs. [2] However, these days most vestibular patients (80%) are still misdiagnosed or receive ineffective treatments. Therefore, it is imperative to improve care for patients with vestibular disorders. This can be facilitated by: standardization of diagnostic tests, obtaining normative values for laboratory tests, and improving the knowledge, skills, and attitudes of individual clinicians and therapists. [1] This thesis aims and enhancing care for vestibular patients by improving several of these factors.

Various high-frequency vestibular tests have been opted over the years to improve the diagnosis of vestibular disorders like Bilateral Vestibulopathy (BV) (**Chapter 1**). The knowledge about these tests was mostly based on healthy subjects and small groups of vestibular patients with unilateral or bilateral loss. Knowledge which is mainly based on healthy subjects and small groups of patients, might have several disadvantages. First, healthy subjects have a "normal" vestibular function, which leads to a linear Vestibulo-Ocular Reflex (VOR) response to high-frequency head movements. This is not always the case in patients with vestibular hypofunction. It is therefore challenging to extrapolate results obtained in healthy subjects, to a patient population. Secondly, small study populations might not be able to represent the whole population. Therefore, to improve (knowledge of) high-frequency vestibular testing, it is important to study larger groups of vestibular patients. This thesis comprises studies with the largest groups of BV patients in the literature regarding the comparison of different VHIT systems (**Chapter 3**, 46 patients), SHIMP testing (**Chapter 4**, 98 patients), and fHIT testing (**Chapter 5**, 23 patients).

Chapter 2 focused on the influence of daily use of corrective spectacles on the Video Head Impulse Test (VHIT) outcomes. The VHIT, and other vestibular tests, are relying on the VOR. The VOR is very adaptive to new situations, such as sudden vestibular loss, but also the influence of prisms and/or corrective spectacles. The VHIT is already included in the diagnostic criteria of BV. [3] However, before this study, it was unclear whether the daily use of corrective spectacles would influence the VOR gain obtained by the VHIT. If so, this might have implications for the interpretation of VHIT results. This study showed no significant differences in VOR gain between the group with or without a refractive error, and between the spectacles and contact lenses group. Furthermore, no correlation was found between VOR gain and refractive error. In conclusion, no corrective measures are necessary when performing the VHIT on subjects with a refractive error, regardless of the way of correction. Hence, during VHIT testing subjects are allowed to wear contact lenses, and it does not matter if subjects wear corrective spectacles right up to the moment of testing.

Chapter 2 also described the effect of consecutive VHIT testing in 16 healthy subjects. Subjects with normal vision were tested six times sequentially, with a good test-retest reliability and no difference in VOR gain between those tests. This demonstrates that repetitive VHIT testing does not influence test outcomes in healthy subjects. **Chapter 3** confirmed these findings in a group of 46 BV patients. No difference in VOR gains and the number of covert saccades were found in this BV population with repetitive testing. This is important knowledge since some research protocols might imply repetitive testing of healthy subjects and/or patients.

A bilateral horizontal VOR gain of <0.6, obtained with VHIT, is one of the main criteria for the diagnosis of BV (**Chapter 1**). The Bárány Criteria do not state which commercially available VHIT system should be used. After all, several VHIT systems are commercially available, each with different methods of VOR gain calculation and different techniques of tracking eye and head movements. These differences, inherent to the systems, might lead to different outcomes and therefore influence BV diagnosis. **Chapter 3** compared VOR gain obtained with three different commercially available VHIT systems (Interacoustics, Otometrics, Synapsys) in 46 BV patients. To reflect routine clinical practice, the data (VOR gain, accepted traces) as provided by the systems, were used. In 17% of the tested BV patients, the three VHIT systems disagreed on the diagnosis of BV (bilateral horizontal VOR gain <0.6). Thus, using different VHIT systems in the same BV patient can lead to clinically significant differences, when using a cut-off value of 0.6 to detect BV. This might hinder the proper diagnosis of BV patients. Nonetheless, BV is diagnosed using a combination of symptoms and several vestibular tests (caloric test, rotatory chair test, VHIT). Since these vestibular tests are complementary, only performing VHIT might not be enough to rule out BV. Furthermore, **Chapter 3** showed significantly lower VOR gains in Synapsys than the other systems. VOR gain between Interacoustics and Otometrics did not significantly differ. The origin of the disagreement between the VHIT systems might have (partially) resulted from inherent differences in the systems themselves, e.g., differences in eye and head tracking. Synapsys uses a ground fixed camera, while Interacoustics and Otometrics use a head-mounted camera. However, it was hypothesized that mainly the differences in the VOR gain calculation algorithm are responsible for the VOR gain differences. [4] This implies that VOR gain outcomes are very sensitive to pre-processing (e.g., desaccading) and interpretation of the traces by the VOR gain calculation algorithm.

The Suppression Head Impulse Test (SHIMP) paradigm was proposed to overcome the challenges of VOR gain calculations, by decreasing the number of covert saccades. After all, covert saccades might lead to artefacts in VOR gain calculation. [5] **Chapter 4** compares SHIMP and HIMP outcomes in 98 BV patients. It was investigated whether SHIMP reduces covert saccades and whether both paradigms agree on diagnosing BV. In this BV population,

SHIMP significantly reduced covert saccades, and almost no covert saccades were observed during SHIMP testing. SHIMP can therefore be considered a "covert saccade killer". VOR gain in SHIMP was significantly lower than in HIMP. However, the clinical implication of this VOR gain difference is most likely small: only a mean difference of 0.02 (leftwards impulses) and 0.03 (rightwards impulses). More importantly, an agreement between HIMP and SHIMP on the diagnosis of BV (VOR gain <0.6) was found in 93% of this population (**Chapter 4**, Table 1). This suggests that the significant differences (presence of covert saccades and VOR gain) observed between SHIMP and HIMP, probably have minor clinical consequences, since both paradigms detect BV in the vast majority of the patients. However, SHIMP could be an alternative in clinical settings which do not have the financial means to obtain a VHIT system. A less expensive diagnostic headband could be used during head impulses, while the examiner observes the presence or absence of overt saccades. [6]

Image stabilization is one of the main functions of the vestibular organs (**Chapter 1**). Patients with BV often complain of oscillopsia (blurred vision during head movements), due to loss of VOR function. The previously discussed tests, HIMP and SHIMP, quantify VOR function using VOR gain. However, a VOR gain does not necessarily reflect functional outcomes and symptomatology. In other words, VOR gain might not correlate with the complaints of oscillopsia in daily life (as measured with e.g., the Oscillopsia Severity Questionnaire). In **Chapter 5**, a new technique to measure the functional performance of the VOR (i.e., visual stabilization abilities), the functional head impulse test (fHIT), was tested on a large group of BV patients. These objective outcomes were compared with the subjective Oscillopsia Severity Questionnaire and the objective Dynamic Visual Acuity test on a treadmill ($DVA_{treadmill}$). Since there is no gold standard for subjectively measuring oscillopsia, this study used the Oscillopsia Severity Questionnaire to capture the subjective complaints of BV patients. Specific questions from this questionnaire – those with the highest correlation with fHIT – could be of value in establishing validated patient-reported outcome measures for BV.

The fHIT and $DVA_{treadmill}$ are very different stimuli (i.e., passive vs. active movements, and only the horizontal semicircular canal vs. all canals and the otoliths). The fHIT correlated better to the Oscillopsia Severity Questionnaire than the $DVA_{treadmill}$, but this correlation was only moderate. Additionally, $DVA_{treadmill}$ showed more "normal" outcomes than fHIT. This could (partially) be attributed to the difference in stimuli, in combination with the residual function of other sensory parts of the vestibular system (i.e., the otoliths and other canals, which are used during $DVA_{treadmill}$ and not during fHIT). During $DVA_{treadmill}$ the patients are possibly able to compensate or adapt during the active head movements, in contrast to fHIT testing using passive head movements. More importantly, a subset of BV patients is unable to walk on a treadmill at 4-6km/h and therefore unable to complete the $DVA_{treadmill}$ test (13-48% respectively), while all patients were able to complete the fHIT (100%). To

summarize, the fHIT seems feasible for quantifying oscillopsia in patients with BV. In the future, it possibly could also be used to measure functional outcomes in patients implanted with a Vestibular Implant. [7]

How to perform a VHIT

Next to investigating specific VHIT outcome measures (VOR gain, covert saccades) and parameters that could influence these outcomes (different commercially available VHIT devices, repetitive testing, etc.), this thesis also implicitly proposes guidelines on how to perform and interpret VHIT traces during daily clinical practice. These are crucial steps to improve the diagnosis of vestibular disorders.

To compare VHIT outcomes within and between subjects, it is of utmost importance to perfectly execute the test, in reproducible conditions. **Chapter 2** described a complete test setup to prevent artefacts, based on literature and expert opinions. Parallel to this research, this test setup was introduced to the Vestibular Laboratory in MUMC+. Furthermore, all examiners were trained extensively, before starting testing patients and/or study participants. As a result, since 2012 all VHITs in MUMC+ are performed by experts using the same test conditions. [8, 9]

After performing the VHIT in a standardized manner, the traces should be interpreted correctly. Firstly, the examiner should be aware of different artefacts and how they appear in raw VHIT traces. [10] Therefore, it remains important to not only assess VOR gain, but also the raw traces and compensatory saccades. **Chapter 4** described how to clean the obtained VOR data based on literature and expert opinion. It defines the prerequisites of proper head- and eye traces. This elaborate description of VHIT data cleaning and processing could be used in future VHIT studies.

Future research

The discrepancy in VOR outcomes between different VHIT systems (**Chapter 3**) is suboptimal for diagnosing vestibular disorders. At this moment, using different VHIT systems in the same BV patient could lead to clinically significant differences in VOR gain, when using a cut-off value of 0.6. When the Synapsys system considered a patient “no BV” (VOR gain ≥0.6) this was always in agreement with both of the other two systems. Nevertheless, the other way around (“BV” with Synapsys and “no BV” in the other two systems) also occurred. It is unknown whether this was a systematic mistake of the Synapsys system, or whether Synapsys was the only system that was able to best detect BV in the high-frequency range of this BV population (all diagnosed with BV according to the Bárány Criteria). This question was beyond the scope of this thesis but should be addressed in the future.

Chapter 4 showed disagreement on the diagnosis of BV between SHIMP and HIMP in only 7% of the patients. These six patients were all diagnosed as BV by SHIMP, and not with HIMP (using the VOR gain calculation of the commercially available VHIT device). These discrepancies could be attributed to VOR gain calculation and cut-off values. Regarding VOR gain calculation, the alternative custom-made algorithm and visual inspection of the traces did show severe vestibular hypofunction in these cases in both paradigms. Although, it must be stressed that also with the custom-made algorithm, no agreement was found between both paradigms in five out of 92 patients. These five patients were not all similar to the six patients mentioned above, which were found with the VHIT device VOR gain calculation method. This implies that VOR gain calculation influences the discrepancy between SHIMP and HIMP findings, but cannot solely be responsible. Other factors like VOR suppression during SHIMP (leading to a lower VOR gain) might also contribute, suggesting that different normative values/cut-off values are needed for SHIMP to determine the presence of vestibular hypofunction. [11] Although no official cut-off values have been published for SHIMP, it was previously proposed to state a lower cut-off value, considering the lower VOR gain values during SHIMP. [12] In **Chapter 4**, lowering the SHIMP cut-off value to 0.5 increased the agreement between HIMP and SHIMP to 97%. However, an increase in the agreement did not imply an increase in the correctly made BV diagnoses. After all, fewer patients were diagnosed with BV after lowering the cut-off value to 0.5, while BV was already demonstrated by caloric testing and/or rotatory chair testing. This demonstrates that most likely more factors are involved, and further research is needed to investigate the origin of the differences in outcomes between VHIT systems. To improve the diagnostic pathway in BV patients, a universal VOR gain calculation algorithm needs to be developed, and a standardized approach to evaluate and interpret head impulse testing outcomes which includes assessment of the raw traces (see above).

At this moment, there is no common treatment to restore the vestibular loss. The vestibular implant seems to be feasible as a therapeutic device for (at least) BV patients. This very promising technique is moving forward, but many aspects are still being investigated or developed before it can be considered a clinically useful medical device. The above-mentioned high-frequency vestibular tests (HIMP, SHIMP, fHIT) might significantly contribute to the evaluation of the efficacy of the vestibular implant in future clinical trials. [13]

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CHAPTER 7

Summary

Summary

Currently, many patients with vestibular symptoms are still misdiagnosed or receive ineffective treatments. Since vestibular deficits are associated with a negative impact on quality of life and an increase in health care costs, improving care for vestibular disorders is essential. This can be facilitated by standardization of diagnostic tests, obtaining normative values for laboratory tests, and improving the knowledge, skills, and attitudes of individual clinicians and therapists. Therefore, this thesis investigated high-frequency vestibular testing, to gain more insights into the diagnostic process of vestibular disorders, more specifically bilateral vestibulopathy (BV).

One of the main functions of the vestibular system is image stabilization, which is facilitated by the Vestibulo-Ocular Reflex (VOR). VOR testing is the hallmark of vestibular testing of the semicircular canals. In **Chapter 2** it was determined whether wearing corrective spectacles causes clinically significant VOR changes during video head impulse testing (VHIT). No significant VOR changes were found. Therefore, no corrective measures are necessary when performing VHIT on subjects with a refractive error.

Chapter 3 demonstrated that different commercially available VHIT systems can result in different VOR outcomes in the same BV patients, leading (in some cases) to disagreement regarding BV diagnosis. Nevertheless, in the majority of the BV patients, the three VHIT systems were in agreement (83%). During VHIT, it remains important to not only assess VOR gain, but also the raw traces and compensatory saccades. Additionally, BV is diagnosed using a combination of symptoms and several vestibular tests (caloric test, rotatory chair test, and/or VHIT). Since these vestibular tests are complementary, only performing VHIT is not always enough to rule out BV.

When comparing Suppression Head Impulse testing (SHIMP) and Head Impulse testing (HIMP) in a large group of BV patients (**Chapter 4**), it was found that almost no covert saccades were produced during SHIMP testing, in contrast to HIMP testing. Moreover, VOR gain was lower during SHIMP testing. However, the clinical relevance of these differences was negligible, since both paradigms were able to detect BV in the vast majority of patients. Therefore, SHIMP testing in clinical practice seems to have little added value in addition to HIMP testing. Nevertheless, since SHIMP demonstrated to be a “covert saccade killer”, SHIMP might be an alternative in clinical settings which do not have the financial means to obtain a VHIT system.

Chapter 5 compared the functional Head Impulse Test (fHIT) and the Dynamic Visual Acuity tested on a treadmill ($DVA_{treadmill}$) with the self-reported complaints of oscillopsia in BV patients (using the Oscillopsia Severity Questionnaire). It was illustrated that fHIT correlated

better than $DVA_{treadmill}$ to subjectively reported oscillopsia, but this correlation was only moderate. Nonetheless, all BV patients were able to complete the fHIT, in contrast to $DVA_{treadmill}$. The findings of this study also implied that fHIT and $DVA_{treadmill}$ are complementary tests of the vestibular system since different stimuli and different parts of the vestibular system are involved.

Finally, to improve the diagnostic pathway in BV patients, it is imperative to standardize high-frequency diagnostic tests, which includes the development of a universal VOR gain calculation algorithm and assessment of the raw traces and corrective saccades. Furthermore, it should be investigated whether VHIT system-specific cut-off values to diagnose BV are a possibility to increase agreement between VHIT paradigms/systems.

CHAPTER 8

Dutch summary –
Nederlandse samenvatting

Dutch summary – Nederlandse samenvatting

Veel patiënten met vestibulaire symptomen krijgen helaas een verkeerde diagnose en/of ineffectieve behandelingen. Aangezien vestibulaire aandoeningen geassocieerd zijn met een negatieve impact op de kwaliteit van leven en stijging van de kosten van de gezondheidszorg, is het verbeteren van de zorg voor vestibulaire aandoeningen essentieel. Dit kan worden bereikt door standaardisatie van diagnostische testen, het verkrijgen van normaalwaarden voor laboratoriumtesten en het verbeteren van kennis, vaardigheden en attitudes van individuele clinici en therapeuten. Dit proefschrift omvat onderzoek naar hoogfrequente vestibulaire testen, om meer inzicht te krijgen in het diagnostische proces bij vestibulaire aandoeningen, in het bijzonder Bilaterale Vestibulopathie (BV).

Een van de belangrijkste functies van het vestibulaire systeem is beeldstabilisatie, dat wordt gefaciliteerd door de Vestibulo-Oculaire Reflex (VOR). Het testen van de VOR staat centraal tijdens het onderzoek van de halfcirkelvormige kanalen. In **Hoofdstuk 2** werd bepaald of het dragen van een corrigerende bril klinisch significante veranderingen in VOR veroorzaakt tijdens Video Head Impulse Testing (VHIT). Er werden geen significante verschillen in VOR gain gevonden. Derhalve zijn er geen corrigerende maatregelen nodig tijdens het uitvoeren van VHIT bij proefpersonen met een refractieafwijking.

Hoofdstuk 3 toonde aan dat verschillende commercieel verkrijgbare VHIT-systemen kunnen resulteren in verschillende VOR-uitkomsten bij dezelfde BV-patiënten, wat (in sommige gevallen) leidt tot discrepanties wat betreft de BV-diagnose. Niettemin waren bij de meerderheid van de BV-patiënten de drie VHIT-systemen het eens over de diagnose (83%). Tijdens VHIT blijft het belangrijk om niet alleen de VOR gain te beoordelen, maar ook de ruwe data en saccades. Bovendien wordt BV gediagnosticeerd door een combinatie van symptomen en verschillende vestibulaire testen (calorische test, draaistoeltest en/of VHIT). Aangezien deze vestibulaire testen complementair zijn, is alleen het uitvoeren van VHIT niet altijd voldoende om BV uit te sluiten.

Bij het vergelijken van de Suppression Head Impulse test (SHIMP) en de Head Impulse test (HIMP) bij een grote groep BV-patiënten (**Hoofdstuk 4**), bleek dat tijdens SHIMP-testen bijna geen covert saccades werden geproduceerd, in tegenstelling tot HIMP-testen. Bovendien was de VOR gain lager tijdens SHIMP-testen. De klinische relevantie van deze verschillen was echter verwaarloosbaar, aangezien beide paradigma's BV in de overgrote meerderheid van de patiënten konden detecteren. SHIMP-testen lijken in de klinische praktijk daarom weinig toegevoegde waarde te hebben ten opzichte van de HIMP-testen. Desalniettemin, aangezien SHIMP heeft aangetoond een "covert saccade killer" te zijn, zou SHIMP een alternatief kunnen zijn in klinische praktijken die niet over de financiële middelen beschikken om een VHIT-systeem aan te schaffen.

Hoofdstuk 5 vergeleek de functional Head Impulse Test (fHIT) en de Dynamic Visual Acuity getest op een loopband ($DVA_{loopband}$) met de zelf-gerapporteerde klachten van oscillopsie bij BV-patiënten (met behulp van de Oscillopsia Severity Questionnaire). Er werd aangetoond dat fHIT beter correleerde dan de $DVA_{loopband}$ test met subjectief gerapporteerde oscillopsie, maar deze correlatie was slechts matig. Tevens konden alle BV-patiënten de fHIT voltooien, in tegenstelling tot $DVA_{loopband}$. De bevindingen van deze studie impliceerden ook dat fHIT en $DVA_{loopband}$ complementaire testen van het vestibulaire systeem zijn, aangezien ze verschillende delen van het vestibulaire systeem activeren.

Ten slotte, om de diagnostiek rondom BV-patiënten te verbeteren, is het noodzakelijk om hoogfrequente diagnostische tests te standaardiseren. Hierbij kan worden gedacht aan de ontwikkeling van een universeel VOR gain algoritme en de beoordeling van ruwe data en saccades. Verder kan worden onderzocht of VHIT-systeem specifieke afkapwaarden voor het diagnosticeren van BV een mogelijkheid zijn om overeenstemming tussen VHIT-paradigma's/ systemen te vergroten.

CHAPTER 9

List of publications and presentations

List of publications

T.S. van Dooren et al. *Suppression Head Impulse test (SHIMP) versus Head Impulse test (HIMP) when diagnosing Bilateral Vestibulopathy*. J. Clin. Med. 2022;**11**:2444

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KNO voorjaarsvergadering 2022

SHIMP vs. HIMP
Poster Barany 2022, Madrid
(e)Poster CI2022, Washington D.C.

Chirurgische interventies evenwichtsaandoeningen
Evenwichtscursus Vaals 2022

Anatomie en (patho-)fysiologie van evenwichtssysteem
International Vestibular Masterclass Utrecht 2022
Onderwijs AIOS KNO UMCG Groningen 2022

Onderwijs HAIOS Maastricht 2021-2022
College bachelor en master studenten Geneeskunde 2017-2022

VHIT versus calorisatie
Leerstoel 25 jaar audiologie Artevelde Hogeschool Gent, oktober 2021

MNGIE, COGAN, Epistaxis na trauma, Glossofaryngeus neuralgie
Regionale refereeravonden OORZON, 2018-2021

The functional Head Impulse Test and oscillopsia in BV patients
Poster CEORL-HNS 2019, Brussel
Poster CI2019, Miami
KNO najaarsvergadering 2018

Comparison of three VHIT systems in diagnosing BV
Bárány Society 2018, Zweden
Poster ARO 2018, Baltimore
Poster MHeNs research day 2018, Maastricht

VHIT and the influence of daily use of spectacles
Poster Bárany Society 2018, Zweden
KNO voorjaarsvergadering 2016

CHAPTER 10

Curriculum Vitae

Curriculum Vitae

Tessa Seline van Dooren was born in Oss on June 18th, 1991. She grew up in Oss with her older brother and parents. In 2009 she graduated from the Titus Brandsma Lyceum and started her medical study at Maastricht University. She started working on vestibular research under supervision of dr. R. van de Berg and prof. H. Kingma during her masters, and continued to do so later during her residency. She spent the last months of her medical study as an intern at the ENT department of Bernhoven Ziekenhuis in Uden and Antoni van Leeuwenhoek Ziekenhuis in Amsterdam. After obtaining her medical degree in 2016, she continued to work at Antoni van Leeuwenhoek Ziekenhuis, until she started her ENT residency at Maastricht University Medical Center in 2017. As part of her residency, she worked for several months in Zuyderland Ziekenhuis in Heerlen and Elkerliek Ziekenhuis in Helmond. In the last year of her residency, she focused on otology and vestibulology. She went back to Zuyderland Ziekenhuis to obtain more experience in otology surgery, and in Maastricht University Medical Center she treated complex vestibular patients in the outpatient clinic together with R. van de Berg. She was also involved in the education of medical students, ENT residents and surgeons, general practitioners and many more professionals in Vestibular Medicine, by giving lectures in the Netherlands and Belgium. Concurrent to her ENT residency, she was able to finish her PhD project. In August 2022 she started a fellowship neurotology in Sint Augustinus Ziekenhuis in Antwerp.

CHAPTER 11

Dankwoord

Dankwoord

Mijn promotor, Raymond. Het is onmogelijk samen te vatten wat jij voor mij hebt betekend deze jaren. Dankzij jou heeft niet alleen mijn promotie, maar mijn gehele carrière vorm gekregen. Dankjewel voor het vertrouwen, ook als ik dit zelf niet had. Dankjewel voor je oneindige geduld, ook al snapte je soms de tranen niet. Dankjewel voor je begeleiding, ook bij nietwerkgerelateerde vraagstukken. En dankjewel, ook voor Roos, voor alle frietjes op vrijdag. Onze wegen scheiden hier niet, ik kijk uit naar de toekomst!

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My saccade buddy, Dmitrii. Thank you for being so patient with me, while trying to interpret raw VHIT outcomes for hours. Your input took these articles to the next level. I enjoyed your wild speculations about the cause of weird-looking traces. Hopefully, someone will find the answers in future research.

Stafleden van de KNO, in het bijzonder mijn opleider: lieve Janny en mijn mentor: lieve Josine. Dank voor jullie steun de afgelopen jaren, ik heb van mijn opleidingstijd genoten. Door de combinatie van *tough love*, maar ook ruimte voor *incontinentie van tranen* hebben jullie mij de kans gegeven deze promotie af te ronden. Jullie hebben mij gevormd, niet alleen als KNO-arts, maar ook als mens.

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