The vestibulo-ocular reflex (VOR) during high-frequency head rotation

Citation for published version (APA):

Meulenbroeks, A. (1997). *The vestibulo-ocular reflex (VOR) during high-frequency head rotation*. [Doctoral Thesis, Maastricht University]. Universiteit Maastricht. <https://doi.org/10.26481/dis.19970627am>

Document status and date:
Published: 01/01/1997

DOI:
[10.26481/dis.19970627am](https://doi.org/10.26481/dis.19970627am)

Document Version:
Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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- The final published version features the final layout of the paper including the volume, issue and page numbers.

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THE VESTIBULO-OCULAR REFLEX (VOR) DURING HIGH-FREQUENCY HEAD ROTATION

Printer: Drukkerij Benda BV, Nijmegen

CIP-gegevens koninklijke bibliotheek, Den Haag

Meulenbroeks, Anna Adriana Wilhelmina Maria

The vestibulo-ocular reflex during high-frequency head rotation

Proefschrift Maastricht.-Met samenvatting in het Nederlands

-Met literatuur opgave

ISBN 90-9010709-6

Trefwoorden: vestibulo-ocular reflex, high-frequency, head rotation

THE VESTIBULO-OCULAR REFLEX (VOR) DURING HIGH-FREQUENCY HEAD ROTATION

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan
de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. mr. M.J. Cohen,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op vrijdag 27 juni 1997 om 12.00 uur

door

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Publication of this thesis was financially supported by:

Acousticon Arnhem, A.C.M Ooms Allergie BV, ARTU Biologicals NV, Astra Pharmaceutica BV, Beltone Nederland, Bloemendal Hoortechneik Arnhem, G.N. Danavox Nederland BV, Electro Medical Instruments BV, Entermed BV, Faazen Hoortoestellen BV, Glaxo Wellcome BV, Hal Allergenen laboratorium BV, Hoechst Marion Roussel BV, Horen Arnhem, Mediprof Medical Products, ReSound BV, Schering Plough BV, Smith Nephew BV, Solvay Duphar BV, Veenhuis Medical Audio BV

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Chapter

1

General introduction

Introduction

Three-dimensional space permits three rotational and three linear degrees of freedom of motion. All these movements are detected by the vestibular system. The system contains two separate components, the semicircular canals (SCCs) and the statolith organs. The SCCs sense angular acceleration and the statolith organs detect linear acceleration as well as rotation. A primary function of the vestibular system is to inform the brain about head and body movement as well as orientation relative to the gravitation vector. Why is this necessary? First, to allow spatial orientation, second to control posture and third to stabilise the eyes in space during fast head movements. The latter is called the vestibulo-ocular reflex (VOR) and enables clear vision under these circumstances. Study of the VOR during high-frequency head rotation is the major theme of research in this thesis.

Man, in common with many other animals, has evolved a powerful system of hierarchical control mechanisms for the stabilisation of the image of the external visual scene on the retina of the eye, thereby ensuring optimal visual acuity during head movements. The afferent information necessary for effective control is derived primarily from the visual system and the vestibular system. However, also auditory and somatosensory information are supposed to contribute.

The primary stimulus for the VOR is acceleration either angular or linear (translational). The responses upon horizontal angular acceleration, mainly considered in this thesis, are elicited and processed in the lateral semicircular canal (LSCC). Here the receptor potential is transferred into action potentials at the level of the first-order vestibular neurons. During acceleration the firing rate of these neurons is proportional to head velocity. These first-order vestibular neurons project from the LSCC to the medial vestibular nucleus and then to the ipsilateral medial rectus nucleus via the ascending tract of Deiters. A second direct excitatory pathway projects from the vestibular nucleus to the contralateral abducens nucleus. From there the signal goes to the contralateral lateral rectus muscle and via the abducens interneurons to the ipsilateral medial rectus motor neurons.¹ This *direct VOR pathway*, consisting of three or four neurons, transmits *velocity* information to the extraocular muscles to ensure that eye velocity matches head velocity (Fig 1).

The final output however, must be an eye position signal, so that both eyes remain stable on the target when the head stops moving. Thus, further integration is needed to convert eye velocity to eye position. The position command is obtained from the velocity command after it arrives at the vestibular nucleus. Integration, in the mathematical sense, of the velocity command to produce the eye *position* command is performed in the medial vestibular nucleus and in the prepositus hypoglossi nucleus.

These two adjacent structures comprise the neural integrator for horizontal eye movements and project to the abducens nucleus and via interneurons to the medial rectus nucleus. This circuit is called the *indirect VOR pathway*.^{2,3}

Figure 1. Pathway of the horizontal vestibulo-ocular reflex pathway in the central nervous system. (HC = horizontal semicircular canal, MR = medial rectus subnucleus of the oculomotor nucleus, MLF = medial longitudinal fasciculus, ATD = ascending tract of Deiters, S = superior, I = inferior, M = medial, L = lateral) Open symbols indicate excitatory neurons, filled symbols indicate inhibitory neurons); figure copied from: Sharpe JA and Barber HO (Eds). *The vestibulo-ocular reflex and vertigo*. New York: Raven Press Ltd. 1993 p 16.

The SCCs are effective in the detection of head rotations of higher frequencies such that eye velocities match head velocity, but they are ineffective at frequencies below about 0.02 Hz.

The vestibular response dies away in case of rotation of the head at constant velocity. During constant velocity head rotation, the cupulae of the SCCs gradually return to the neutral position with a time constant of about 5-7 seconds, which implies that the response will be zero after 15-20 seconds. The firing rate of the vestibular neurons, which varies with the angle of deviation of the cupulae, incorrectly informs the brain that the head is moving at progressively lower velocities. This limitation of the SCCs

to detect low frequencies is partly compensated by *velocity storage*, located in the prepositus hypoglossi nucleus, with the participation of the vestibular nuclei and the cerebellum. The velocity storage mechanism uses the peripheral vestibular signal and by the process of integration, in the mathematical sense, increases the frequency range of the VOR threefold. That is, the time constant of decay of vestibular nystagmus is prolonged to about 20 seconds, three times longer than the signal actually delivered from the SCCs. During sinusoidal rotation of the head the velocity storage mechanism is loaded and after head rotation this is supposed to account for the so-called head shaking nystagmus in case of unilateral vestibular dysfunction.

Vestibulo-ocular reflex (VOR)

The function of the VOR was already subject of discussion in the previous century: "The vestibulo-ocular reflex is an integral part of a complex control system which maintains targets on the fovea by repositioning the eyes during voluntary and involuntary head movements" (Crum Brown, 1874).⁴ The VOR is generally supposed to serve vision by generating conjugate smooth eye movements that are approximately equal in velocity and opposite in direction to head movements, so that the eyes, to a great extent, are stabilised in space whilst the head is in motion. Consequently, objects fixed in space may be viewed without smearing of the retinal image during normal locomotor activities. In most textbooks it is suggested that the VOR only consists of versional eye movements. However, recently new insight has appeared considering the impact of the vestibular system with respect to conjugation, version and vergence.^{5,6} These aspects will not be discussed in this thesis.

Visual acuity to some extent, depends on the accuracy of vestibular mediated smooth eye movements.⁷ As the eyes and the head move in opposite direction, the phase of the VOR must be such that the eyes are 180 degrees out of phase with the head. By convention this phaseshift of the VOR is then considered to be optimal and 0. The ratio of eye velocity and head velocity, the VOR gain, must approximate unity.

Slippage of the images on the retina with velocities exceeding 2-3 degrees per second blurs visual acuity.^{8,9} If the gain of the reflex deviates too much from the ideal value of 1.0, the retinal image slips off the fovea, although it may be transiently stable on the retina. If eye velocity leads head velocity (phaselead) or if eye velocity lags head velocity (phaselag) the target image will not be stationary on the retina for the major time of exposure. Saccades or nystagmus quick phases opposite to vestibular smooth eye movements are dispatched to bring the fovea toward a *new* target when the VOR is unable to stabilise the original target. Insufficiency of the VOR causes nystagmus and dizziness even when the head is stationary in space. Abnormalities of gain or phase

cause visual blurring, oscillopsia and dizziness when the head is moving.

The frequency range in which the VOR functions, can be divided in low (< 1 Hz) where the visual system dominates^{10,11}, intermediate (1-3 Hz) where the visual and the vestibular system interact, and the high frequencies (> 3 Hz) where the vestibular system dominates.¹²

In the low frequency range the optokinetic-pursuit system is largely responsible for maintaining gaze, with retinal image slip being the stimulus responsible for driving the system. However, some discussion has risen about this recently again.^{12,13} The maximal pursuit speed of the retino-ocular reflex is 60-70 degrees per second as shown in the adaptation limit of the optokinetic nystagmus. At target frequencies above 0.5 Hz the effectiveness of the smooth pursuit system already declines.¹⁴

During high-frequency head movements as occur during walking or running, the VOR requires a short latency response to prevent degradation of images, due to retinal image slip. Smooth pursuit and optokinetic visual following responses are too slow to enable clear vision during fast head movements. The latency being about 75-100 msec for smooth pursuit and 70 msec for optokinetic tracking in humans.^{15,16} The latency of the VOR has been reported to be less than 16 msec^{17,18,19,20}, but recently Tabak et al. found latencies of 3.5 msec at 2 Hz and 6 msec at 6 Hz.^{21,22,23} Reduction of the latencies occur with increased frequency of stimulation and increased alertness.²⁴

Since the introduction of rotatory testing for clinical vestibular analysis by Bárány (1907), numerous attempts have been made to develop rotatory tests capable of extracting quantitative information from VOR measurements.²⁵ In order to show the "pure" VOR in the low and intermediate frequency range it was generally assumed that no visual information should be available to the subject during the tests. Usually this is accomplished by rotating the subject in the dark. The underlying assumption of the tests was, that passive (whole body) rotation in darkness would generate compensatory eye movements which were exclusively evoked by input from the SCCs and thereby indicative of vestibular function. It has been shown however, that in absence of visual information, the VOR measurements suffer from reproducibility and are strongly influenced by the instructions given to the subjects and their state of alertness. The VOR in the dark is markedly influenced by subjective factors and gain can be changed at will, from 0.35 to 0.95, by imagining a visual target moving with the head, or imagining it earth fixed respectively.^{26,27,28,29,30,31,32} Other mechanisms can also modify the VOR, for example habituation and adaptation to new stimuli (magnifying glasses and left-right reversal).³³ Instruction and alertness were found to be less relevant in the high-frequency range.^{34,35} Larsby et al. did not find any influence of instructions between 0.2-4.5 Hz, while McKinley & Peterson did find only a slight influence in the frequency range of 0.25-1.9 Hz.^{34,36}

Another disadvantage of the usual clinical rotatory tests employed is, that they are conducted at oscillation frequencies only up to 0.5 Hz. The 0.5 Hz limit is caused by torque limitations in the motor driving the chair, but even more by problems concerned with head and body fixation.³⁷ Those frequencies are well below those present in most active and passive head movements in every day activities, which can reach values up to at least 6 Hz. During running, the predominant frequencies of head rotations may even range as high as 8 Hz, with significant harmonics up to 15 Hz, mainly in the vertical plane.^{38,39} Therefore, thanks to the mechanical properties of the SCCs, the optimal frequency response of the VOR ranges from 1-10 Hz close to these physiological requirements.^{40,41,14,15,16} All these aspects plead for the development of tests of the VOR in the higher frequency range.

Quantification of the specific vestibular contribution to compensatory eye movements in the light appears to be possible provided the rotatory acceleration exceeds the dynamic range of visual tracking. A fairly recent development is characterised by both active and passive high-frequency head rotation tests.^{42,43,44} The advantage of these tests is, that no expensive rotatory chair is necessary and results so far have been promising. O'Leary et al. even postulate, that the active Vestibular Autorotation Test (VAT) allows discrimination between patients with an acoustic neuroma and Meniere's disease from subjects with a normal ear; also the side and size of the acoustic neuroma might be detected by the VAT.^{45,46,47} O'Leary et al. studied the VOR during *active* head rotation, using Electro-Oculography (EOG) and a rate sensor on a headband. Tabak et al. were the first to quantify the VOR during high frequency *passive* head rotation up to 20 Hz, using a specially designed headshaker and measuring eye and head movements by means of magnetic search coils.^{21,22,23}

Experimental set-up

The aim of this research project was to develop, to improve and to evaluate tests for quantification of the VOR during high-frequency head rotation.

In all our high-frequency head rotation experiments subjects were seated and asked to focus on a fixed yellow target on a television screen (black background) 1 meter in front of them. A distance of 1 meter theoretically results in a 10% higher gain compared to accommodation at infinity, and a 3% higher gain compared to accommodation at 1.5 meter.⁴⁴ We started our research project using the active high-frequency head rotation test or VAT in normal subjects (Chapter 2).

Head velocity was detected by an *angular rate sensor*. At first this rate sensor was

attached to a *headband* (Fig 2), but later to a *biteboard* (Fig 3). Carefull observation of the subjects during the experiment with the headband and analysis of the data gave the impression that, due to the inertia of the head band, slippage occurred which might introduce inaccuracies in detection of head velocity, which was an important issue of investigation. This problem was overcome by using a biteboard.

It was often impossible for healthy subjects to reach high rotation frequencies during *active* head rotation. Therefore, a *passive* high-frequency head rotation test was optimised and evaluated, first in normal subjects (Chapter 3) later in patients (Chapters 4 and 5). Passive head rotation was achieved by using a computer driven headshaker according to the original idea of Collewijn (Rotterdam, The Netherlands).^{21,22,23} This is a new technique based on a helmet with torque motor, which oscillates a mass and through that the head (Fig 4).

Figure 2. Angular rate sensor on headband.

Figure 3. Angular rate sensor on biteboard.

Finally, we investigated the ability of high-frequency testing to evaluate and quantify the effect of an antivertiginous drug upon the VOR (Chapter 6).

EOG does have background noise level, which is a limiting factor in the analysis of especially pseudorandom stimuli at low intensities or high frequencies (above 4 Hz the amplitude of the induced eye velocities is small). To counteract this aspect to some extent, the high-frequency head rotation test was therefore done in the light because *EOG* (corneoretinal) potentials increase with light intensity.⁴⁷

Figure 4. Helmet with torque motor for passive head rotation.

In a pilot study using 5 normal subjects we compared the *scleral coil technique (SCT)* with EOG for detection of eye velocity. Scleral coils were placed on the eye and a homogeneous magnetic field was generated around the subject.⁴⁸ The position of the eye in the magnetic field can then be measured precisely. Simultaneously eye position relative to head position was measured by EOG. Eye velocity was calculated by digital differentiation of the original eye position signals. Head velocity was detected by an angular rate sensor on a biteboard.

Before the comparison of SCT and EOG could be performed properly, several problems had to be solved. First, the EOG electrodes detected the electromagnetic field that was induced by the scleral coil equipment. Twisting and shielding of the electrode wires reduced this effect sufficiently to allow a proper detection of the corneoretinal potentials without substantial interference with the magnetic field. The torque motor was found to have no influence on the magnetic field, the scleral coil signals or EOG.

The gain of the VOR is somewhat overestimated using EOG compared to SCT at all frequencies under survey (Fig 5). This is significant at 2, 3 and 6 Hz. Interindividual variability was greater using EOG compared with SCT. We concluded that EOG allows detection of the VOR at high frequencies, especially between 2-4 Hz, although with a somewhat limited accuracy. EOG is more patient friendly and more easy to use in the clinic and could facilitate a broad clinical application of high-frequency testing. Therefore we decided to continue our study by using EOG.

Figure 5. Gain (2 standard deviations) related to frequency; electro-oculography versus scleral coil technique (n = 5).

A *sinusoidal stimulus* was used in this research project although pseudorandom stimulation is generally preferred above sinusoidal stimulation, because it is supposed to exclude optimisation of the VOR by prediction and anticipation, although Furman et al. found no measurable difference between the results obtained by pseudorandom and sinusoidal stimuli in the rhesus monkey.^{49,50,51} Nevertheless we were forced to apply predictable sinusoidal stimuli in the present study because we observed that the gain, phase and coherence of the VOR using pseudorandom multifrequency passive high-frequency head rotation could not be detected with sufficient reproducibility in the pilot study described above. The major problems in case of multifrequency stimulation appeared to be: *i.* the poor transfer of the stimulus upon the head (limitation of helmet to head coupling) which induced irregular stimulus patterns and *ii.* the artefacts induced by the motor (induction) and the electrode movements upon the EOG registration. In contrast, pure sinusoidal stimulation allowed sufficient filtering and frequency specific analysis for artefact rejection to improve the signal-to-noise ratio.

Contents of this thesis.

This thesis contains five chapters which were originally written as separate manuscripts. Below a brief description of the contents of the chapters is given.

Chapter 2: Vestibular Autorotation Test (VAT).

The VAT, a high-frequency active head rotation test, can be considered as a very attractive method to quantify the VOR in the higher frequency range because of the short test duration and the low costs involved with the apparatus. We investigated the reproducibility and clinical applicability of the VAT in normal subjects and quantified the gain and phase of the VOR between 2-6 Hz using various techniques to detect head angular velocity.

Chapter 3: Active versus passive high-frequency head rotation.

Although the subjects studied in Chapter 2 were young and healthy individuals, and in spite of intensive support, it was often impossible to reach high frequencies during active head rotation. As a consequence we started to use a computer-driven headshaker according to the original idea of Collewyn by which the head could be rotated passively up to 6 Hz.^{21,22,23} Results obtained by active and passive high-frequency stimulation were compared.

Chapter 4: Passive high-frequency head rotation in patients with Meniere's disease.

Meniere's disease is generally considered as an inner ear disorder resulting in a classical triad of symptoms of attacks of vertigo, unilateral sensorineural hearing loss and tinnitus. There appears to be a great variability of the outcome of the two most frequently applied vestibular function tests in patients with Meniere's disease. As many as 30-50% of the patients show normal responses to caloric stimulation.^{52,53} In some studies normal caloric test results and abnormal rotational chair test results are reported, or vice versa.^{54,55} The poor correlation between complaints and vestibular test outcome might have been the major argument not to use the outcome of these low-frequency vestibular function tests for the disease classification (AAO-HNS criteria).⁵⁶ As the passive high-frequency head rotation test had proven reproducible and well applicable this test was applied in 20 patients with Meniere's disease to quantify their high-frequency VOR.

Chapter 5: Passive high-frequency head rotation in patients with bilateral vestibular impairment.

From clinical observations it is well known that patients show a remarkable ability to compensate for loss of peripheral vestibular sensitivity.^{57,58} The assessment of residual vestibular function in patients with suspected bilateral impairment is a major clinical

problem. Caloric irrigation is equivalent to a very low-frequency stimulation of the VOR, approximately 0.003 Hz.⁵⁹ Consequently, it can be anticipated that the results of caloric testing and high-frequency rotation test will not agree in all cases of vestibular disease. More specific, an absence of caloric response does not indicate absence of vestibular function. As a consequence of our previous studies we studied 8 patients with chronic, compensated, bilateral vestibular impairment, resulting in bilateral reduced or absent caloric responses. The VOR characteristics of these patients were assessed by the passive high-frequency head rotation test. The question addressed was: does the high-frequency VOR reveal the functional status of the patients?

Chapter 6: The passive high-frequency head rotation test as a tool to quantify the effect of betahistine.

In the previous chapters it was investigated whether high-frequency head rotation tests might inform us more about the vestibular function than standard vestibular tests. Betahistine is known to affect vestibular function and to reduce complaints but the effect of the drug upon the low-frequency VOR is still subject of investigation (conflicting results). In this chapter we investigated whether betahistine might change the high-frequency VOR. In order to increase sensitivity this double-blind placebo controlled study was performed only in those patients that suffered from paroxysmal vertigo and who indicated that their complaints markedly reduced by betahistine treatment.

Chapter 7: General discussion

In this chapter the results of research described in this thesis is discussed in general terms.

Chapter 8: Summary in Dutch

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Chapter

2

**Quantitative evaluation of the
Vestibular Autorotation Test (VAT)
in normal subjects**

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Acta Otolaryngologica (Stockh) 1995;Suppl 520:327-33.

ABSTRACT

The Vestibular Autorotation Test (VAT) is a relatively easy method for testing the Vestibulo Ocular Reflex (VOR) at higher frequencies by asking the patient to actively rotate his/her head from side to side (yaw) with increasing frequency. In this study we investigated reproducibility and clinical applicability of this method and quantified gain and phase of the VOR in normal subjects. We studied the VOR in 33 subjects over a frequency range from 2 to 6 Hz. Ten Subjects were investigated with an angular rate sensor mounted on a headband. In this group the velocity gain tended to decrease at higher frequencies and phase lag increased slightly. In a second experiment (2 subjects) head velocity was detected simultaneously by a angular rate sensor fixed to a headband and an identical sensor attached to a biteboard. It was shown that the gain of the VOR in the first group was underrated and phase shift was overrated due to slippage of the headband fixed rate sensor. Therefore in a third experiment 21 subjects were investigated with the rate sensor attached to a biteboard only. In this group VOR gain was close to unity and phase was close to 0° (180° out of phase) from 2 up to 6 Hz. In contrast to other studies a considerable number of subjects was unable to reach rotation frequencies above 4 Hz. Our results agree with those of recently published results and disagree with others, both using a headband. This is interpreted as due to difficulties in sensing head velocity accurately. Conclusion: vestibular autorotation is an accurate and reproducible way of testing the high-frequency range of the vestibulo-ocular reflex, provided that head velocity is measured by a biteboard.

INTRODUCTION

Natural head movement frequencies, for instance during walking, range from about 1 to 4 Hz. Testing the Vestibulo Ocular Reflex (VOR) in this frequency range is not only attractive because it reveals the physiological range of natural head movements, but also because the visual ocular control (smooth pursuit) in this frequency range is generally considered small. Eye movements are not affected by visual information during head movements exceeding approximately 2 Hz.¹⁻⁴ However, the VOR is seldomly tested in this frequency range because of technical limitations of most rotational chair systems and problems concerned with head and body fixation.⁵ A relatively easy method for testing the gain and phase characteristics of the VOR is the Vestibular Autorotation Test (VAT) in which the patient is asked to shake the head actively. The great advantage of this test seems to be that it makes it possible to measure the VOR at higher frequencies up to 6 Hz. Tomlinson et al. seem to be the first to describe this method of testing and later Fineberg et al. and O'Leary et al.^{6,7,8,9,10} The latter also postulates that the VAT allows discrimination between an acoustic neuroma and Meniere's disease from a normal ear; also the site (left, right) and size of the acoustic neuroma might be detected by using the VAT. Other attractive aspects of this technique are the short test time and the low costs of the apparatus (no expensive rotatory chair).

The purpose of this study was to investigate the reproducibility and clinical applicability of the VAT in normals and to quantify the gain and phase of the VOR between 2-6 Hz.

MATERIAL AND METHODS

A total of 33 healthy subjects were studied. They had no history of balance, hearing or neurological disorder or neck complaints. All subjects were instructed not to drink alcohol or take any drugs for at least 24 hours before the test. Each test lasted approximately 20 seconds. Subjects were seated and asked to focus on a fixed black target of 0.5° on a white wall 1.0 meter in front of them. Subsequently they were asked to move their head smoothly from side to side in synchrony with a click, of which the repetition frequency linearly increased from 0.5 to 6 Hz in 20 s. After informed consent, subjects were given verbal instructions and one or more practice sessions before the actual recording was established. Head rotation was considered optimal by visual observation of the quality of head movement. The test was performed three times in each subject to check reproducibility. Horizontal eye movements were recorded by Electro-Oculography (EOG), with bilateral electrodes positioned on the outer canthi, vertical eye position was recorded with electrodes above and below the right eye; a reference

electrode was positioned on the forehead above the bridge of the nose. Vertical eye position was recorded to detect eye blinking.

Prior to each test the horizontal EOG-lead was calibrated by predictable saccades of 20° visual angle (distance 1 meter, target size 0.5 degree, black target, white background). Ambient light intensity in the investigation room was 10 Lux. Horizontal and vertical eye position and head velocity were filtered analogous (low pass 30 Hz, 12 dB/oct) fed into a computerised electronystagmograph (Nystagliner, Toennies, Wuerzburg) for raw data storage and signal analysis. The VAT is default implemented in this computersystem.

Data-acquisition occurred at a 5 kHz sampling rate to minimise time shifts between the sequentially sampled channels. Data-storage occurred after resampling resulting in 100 datapoints per channel per second. Automatic elimination of eye blinks and saccades, calculation of eye velocity, calculation of velocity gain, phase and coherence are described in detail elsewhere, but can be summarised as follows: data were first digitally differentiated without introducing a phase shift by differencing neighbouring samples (3 points differentiation) followed by smoothing taking the running average with unit weights.¹¹ Then high velocity components (eye blinks and saccades) were eliminated by applying a non linear median filter with a filter width of 0.050 s (5 datapoints).¹²

These filter techniques essentially change the amplitude in a frequency-dependent way.¹³ However, correction was not considered, because no transfer function of these non-linear filters are available and because computer simulations using artificial signals did not show any detectable inaccuracies of the analysis. Subsequently a fast Fourier transformation over a Welch window (to reduce leakage) of 512 points was performed calculating gain, phase and coherence comparing eye velocity with head velocity. After each calculation the 512 window was shifted over 256 points, resulting in overlapping segments, and the result of the gain, phase and coherence was then averaged over the frequencies detected. In case of asymmetrical saccades, removing fast components introduces a shift of the signal average. The resulting peak at the first frequency bins of the spectrum could obscure the sought response at the lowest frequency bins, and therefore any offset of the mean was neutralized before Fourier transformation. Frequency peaks were detected automatically. Peaks were traced if the spectrum had sufficient relief: the highest value should be more than 100 times the lowest value (preventing analysis of noise). Next any local (current position ± 1 bin) maximum was required *i.* to be above the threshold of 10% of the maximum of the spectrum and either *ii.* to be at least twice as high as the local (current position ± 5 bins) minima at both sides, or *iii.* to be at least twice as high as the local minimum of one side and to be of about the same height as the local maximum of the other side. Condition 1 selects against noise peaks, condition 2 against noise shoulders, condition 3 retains twin peaks nevertheless.

In our experiments the subject was voluntarily shaking his/her head, which, although guided by an auditory stimulus, resulted in various frequency peaks at which gain, phase and coherence were calculated. The spectral content, and therefore the location of the frequency peaks, appeared to vary considerably. In the literature it is not always clear how other authors solved this problem methodically.^{7-10,14} In order to allow comparison between successive measurements (reproducibility) and subjects (inter-subject variance) the frequency response at 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5 and 6 Hz were calculated from the spectrum by linear interpolation and extrapolation. This procedure was only performed within the range of the actual frequency spectrum calculated, and was not allowed to yield frequency responses more than 0.5 Hz outside this spectrum. Mean gain, phase and standard deviation (SD) of each of subject's three tests were calculated. At each frequency response obtained in this way, mean gain, phase and SD of each of subject's three tests were calculated.

From these values we calculated mean gain, phase and SD of the two groups. Coherence function was also calculated to assess the validity of the data and to give an indication of the linear dependence between input and output.

Experiment 1

In a group, consisting of 10 subjects (age ranging from 23 to 47 years with a mean of 28 years), each subject was fitted with an adjustable light weight headband containing a calibrated angular rate sensor (Watsons Ind.), which detected the angular head velocity in the horizontal plane. The angular rate sensor was situated 5 centimeters above the head and coincided more or less with the rotation axis of the cervical spine (the secant defined by the frontal plane through a point 1 cm anterior to the external auditory meatus and the sagittal plane was used as an indicator for the location of the cervical spine rotation axis). This method was more or less equivalent with that of Fineberg et al. and O'Leary et al.^{7,8,9,10}

Experiment 2

Careful observation of the subjects during experiment 1 and analysis of the data gave the impression that, due to the inertia of the head band, slippage occurred which might introduce inaccuracies in detection of head velocity. We experienced similar problems in previous experiments with high-frequency whole body rotation (see also Hydén & Schwarz¹⁵) which might introduce errors in the calculation of velocity gain and phase of the VOR.

We therefore expanded the series by measuring gain, phase and coherence in 2 subjects with detection of head velocity simultaneously with the headband fixed rate sensor and a second biteboard fixed identical rate sensor. The result of this second experiment confirmed the hypothesis that head velocity is detected more accurately with a biteboard fixed angular rate sensor.

Experiment 3

The series were therefore expanded with a group of 21 subjects (age ranging from 1 to 54 years with a mean of 34 years). Now angular head velocity was detected by using only a small biteboard to which the same angular rate sensor was attached. This method was equivalent with that of Tomlinson et al.⁶

RESULTS

Although the subjects were young and healthy individuals, and in spite of intensive support, it was often impossible to reach a high headshaking frequency especially in the first experiment. Only 2 subjects (20 %) of the headband group and 11 subjects (52 %) of the biteboard group reached a frequency of 5.5 Hz. Six Subjects (60 %) of the first group and 8 subjects (38%) of the second group were not able to reach a frequency of 4.5 Hz (Table I). The gain of the VOR depends on the accommodation distance.⁶ We applied a distance of 1 meter which theoretically results in a 10% higher gain compared with accommodation at infinity, and a 3% higher gain compared with accommodation at 1.5 meter.⁷⁻¹⁰

Table I. Percentage of subjects reaching each frequency,
HB = headband group, BB = biteboard group.

freq	2	2.5	3	3.5	4	4.5	5	5.5
HB (n = 10)	100	100	100	60	60	40	20	20
BB (n = 21)	100	100	95	76	76	62	57	52

In Fig 1 mean gain (top), mean phase (bottom) ± 2 SD related to rotation frequency of the headband group and biteboard group are shown. In the headband group gain tended to decrease with increasing frequency (0.86 at 2 Hz, 0.90 at 3.5 Hz and 0.66 at 5.5 Hz). Phase tended to decrease until 4 Hz and then to increase again. In Table II the numerical data are shown.

Quantitative evaluation of the Vestibular Autorotation Test (VAT)

Figure 1. Gain (top) and phaseshift (bottom) (± 2 SD) related to frequency for headband group versus biteboard group.

In the biteboard group gain stayed close to unity (1.07 at 2 Hz, 1.05 at 3.5 Hz and 1.02 at 5.5 Hz) with increasing frequency. VOR phase did not significantly change with frequency either. In Table III the numerical data of the biteboard group are shown. Coherence was above 0.93 even at higher frequencies in both groups.

Table II. Mean gain, mean phase, SD and range of 10 subjects with headband.

freq	mean gain	SD	range	mean phase	SD	range
2	0.86	0.03	0.74 - 1.03	-5	2	-18 - -1
2.5	0.86	0.04	0.73 - 1.09	-5	2	-23 - -4
3	0.87	0.04	0.72 - 1.18	-7	4	-28 - 8
3.5	0.90	0.05	0.74 - 1.19	-11	10	-35 - -4
4	0.90	0.08	0.68 - 1.27	-9	7	-43 - 6
4.5	0.72	0.06	0.60 - 0.88	4	7	-18 - 6
5	0.74	0.04	0.70 - 0.77	17	1	4 - 5
5.5	0.66	0.04	0.64 - 0.69	13	6	-5 - 4

Table III. Mean gain, mean phase, SD and range of 21 subjects with biteboard.

freq	mean gain	SD	range	mean phase	SD	range
2	1.07	0.04	0.70 - 1.60	-1	1	-18 - -1
2,5	1.08	0.05	0.70 - 1.73	-1	1	-18 - -6
3	1.09	0.05	0.70 - 1.84	-2	1	-17 - -1
3.5	1.05	0.05	0.67 - 1.45	-3	1	-24 - -5
4	1.07	0.05	0.67 - 1.51	-3	2	-38 - 4
4.5	1.03	0.06	0.67 - 1.54	-3	3	-42 - 4
5	1.04	0.06	0.66 - 1.57	-1	4	-46 - -2
5.5	1.02	0.08	0.66 - 1.60	-1	4	-5 - 4
6	1.03	0.12	0.66 - 1.80	-2	7	-58 - 5

DISCUSSION

Reproducibility

In each subject the VAT was performed three times. Table 2 and 3 show that SD values of the gain of all subjects range from 0.04 to 0.12. SD values however, of each subject's three tests range from 0.01-0.04 at all frequencies. This indicates, that intraindividual variability for gain values is much smaller than interindividual variability. However, this was less pronounced for phase values. Variability had a tendency of increasing with increasing frequency, comparable with the results of O'Leary et al.^{8,9,10} These values indicate that the VAT is a successfully reproducible test.

Frequency response.

Fineberg et al. and O'Leary et al., who used a headband with velocity sensor, found a marked decrease in gain at higher frequencies: from 0.9 at 2 Hz to 0.7 at 6 Hz approximately and this is comparable to our headband group.^{7,8,9,10} Hoshowski et al. however, also performed a VAT with an angular rate sensor attached to a headband and found a gain close to unity up to higher frequencies.¹⁴ They observed a mean gain ranging from 0.92 - 0.94 in all frequencies between 2 and 4.3 Hz. In a previous publication the same group reported similar results with a small, not significant decrease of the gain at 5-6 Hz using a biteboard as we did in our second and third experiment.⁶

The phaselag found by Fineberg et al. and O'Leary et al. at higher frequencies could not be reproduced in our study.^{7,8,9,10} Phase was constantly zero in the study of Tomlinson et al. and agree very well with the results obtained in our biteboard group.⁷ If we assume that head velocity is detected more accurately with the biteboard fixed sensor, which seems to be very likely, these experiments suggest that the decrease of gain and the increase of phase lag with increasing shaking frequency in the headband group might be due to inaccurate detection of head velocity. The third experiment indeed shows that VOR gain and VOR phase are close to 1.0 and 0° respectively over the whole frequency band between 2 and 6 Hz.

Comparison of our data with high-frequency whole body rotation introduces some interpretation difficulties. First, theoretically a difference might exist between active and passive head rotation, and between head and whole body rotation. In many studies it appears that response is optimal if subjects control their own movement and/or can anticipate or predict the movements to come. Therefore we should expect that our results obtained with active head shaking might show a more optimal VOR than results obtained from passive whole body rotation or passive head shaking.

In case of whole body rotation no cervical input to the vestibular system is achieved; at high frequencies, however, other diffuse tactile, proprioceptive information reaches the brainstem which contributes to the perception of movement of the body or body

components and may affect the VOR gain and phase. However, the Cervico-Ocular Reflex (COR) seems to be effective at low stimulus velocities, low frequencies and in patients suffering from bilateral labyrinthine deficits and is minimal or even completely absent in normal subjects and is therefore supposed to have contributed not or minimally to the responses we detected.^{17,18}

During whole body rotation at frequencies above 0.5-1 Hz, head and trunk movements may differ considerably due to poor fixation of the various body components. Some studies report an increase in gain up to 4 in higher frequencies.^{15,19,20} In these studies however, eye velocity was compared with chair velocity instead of head velocity. This might be the reason why gain was somewhat overrated. Hoshowski et al. however, measured gain during passive high-frequency whole body rotation with an angular rate sensor attached to a headband, thus comparing eye velocity to head instead of chair velocity.¹⁴ They also found an increase in gain: 1.0 at 2 Hz increasing up to 1.7 at 4 Hz. They suggested that cervical input during active head rotation may contribute to a more accurate estimate of the VOR gain. However, Kasteel van Linge & Maas detected eye position with the scleral coil technique and they mentioned that above 5 Hz, during passive whole body rotation, head and eye amplitude reach values of only 1° amplitude which is at the maximum resolution of EOG and therefore makes an accurate detection of VOR gain and phase at these frequencies doubtful with whole body rotation.²¹ Recently Tabak et al. reported that the gain of the VOR detected with the scleral coil technique, using a headshaker, remained near unity between 2 and 6 Hz.²² Preliminary results in our laboratory with a headshaker developed after Collewijn with the use of EOG confirm their results and show that gain of the VOR between 2 and 6 Hz remains near unity and that phase lag increases slightly.²² This might indicate that the large increase of gain during whole body rotation does not at all reflect processes dealing with vestibular input.

Frequency range.

In our study it appeared that 60% of the subjects in the headband group and 38 % of the subjects in the biteboard group, did not reach a rotation frequency of 4.5 Hz despite of intensive support. The difference might be due to the fact that the headband is less comfortable and slips along the head compared with the steady fixed biteboard. This explanation is confirmed by the subjective sensations of the subjects. However, in the study of O'Leary et al. and Tomlinson et al. all subjects reached a frequency of 6 Hz.^{6,8,9,10} The study of O'Leary et al. of age-related responses of the VOR shows that head movements in some subjects of the elderly population were generally slower (less than 4 Hz).⁹ We could not confirm that the majority of normal subjects can reach frequencies up to 6 Hz. These conflicting results might be explained by differences with respect to training and subjects but also by the fact that the frequency analysis used by O'Leary differs from ours.

The limited frequency range we encountered in our study might not be a very important problem because several studies already suggest that other factors might invalidate the high frequency results. Larsby studying passive whole body rotations mentioned that EOG recording is a limiting factor at high frequencies.²³ Signal-to-noise ratio decreases due to reduced power in high frequencies. Another factor is that above 3.5 Hz in the study of Larsby et al., coherence is less, indicating a non-linearity in the system. Larsby et al. propose to measure the VOR for clinical purposes between 2.5-3.5 Hz because of a reduced non-vestibular influence on the VOR and the relatively good responses. Artefacts are also introduced by electrodes that move relatively to the skull at higher frequencies.

The aspect of reaching a limited frequency range in case of active rotation has been overcome recently by Tabak et al. using a computer driven headshaker which is able to rotate the head passively up to 20 Hz.²²

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Chapter

3

**Quantification of the vestibulo-ocular
reflex in normal subjects:
active versus passive
high-frequency head rotation**

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Otorhinolaryngologica Nova 1995;4:325-33 (in German).

ABSTRACT

Since the introduction of rotatory testing for clinical vestibular analysis by Bárány (1907), numerous attempts have been made to develop rotatory tests capable of extracting quantitative information from Vestibulo-Ocular Reflex (VOR) measurements.¹ Most clinical rotatory tests are conducted at oscillation frequencies up to 0.5 Hz, although head movements during activities in daily life can reach values up to 8 Hz.

This study compared VOR characteristics of active versus passive high-frequency head rotation up to 6 Hz in young healthy subjects. During active head rotation gain stayed close to unity and a small phaselead existed in the whole frequency range. However, not every subject reached 6 Hz. During passive head rotation, by means of a computer driven headshaker, gain decreased to 0.82 at 6 Hz but phaseshift was 0° at all frequencies applied. Our present work is focussed on quantification of the VOR during active and passive high-frequency head rotation in various patient groups suffering from vertigo. We hope to be able to make a distinction between patients and normal subjects by means of one of the tests described. Especially the active head rotation test is a cheap and easy applicable method in the clinic and might be an attractive alternative for an expensive rotatory chair.

INTRODUCTION

"The VOR is an integral part of a complex control system which maintains targets on the fovea by repositioning the eyes during voluntary and involuntary head movements".²

Man, in common with many other animals, has evolved a powerful system of hierarchical control mechanisms for stabilisation the foveal image thereby ensuring maximal visual acuity. The afferent information necessary for effective control is derived primarily from two sources; the visual system and the vestibular apparatus, but also from somatosensory information. Over the last three decades considerable attention has been paid to the vestibular system in order to gain insight in the neural mechanisms mediating the VOR. Since the introduction of rotatory testing for clinical vestibular analysis by Bárány, numerous attempts have been made to develop rotatory tests capable of extracting quantitative information from VOR measurements. However, most clinical rotatory tests employed are conducted at oscillation frequencies up to 0.5 Hz. The 0.5 limit is set by torque limitations in the motor driving the chair and problems concerned with head and body fixation.³ Those frequencies are well below those present in most active and passive head movements in everyday activities, which can reach values up to at least 6 Hz. During running, the predominant frequencies of head rotations may even range as high as 8 Hz, with significant harmonics up to 15 Hz.^{4,5} In this frequency range gaze is principally controlled by the VOR, whereas in the lower frequency range, the visual control system also has a large influence.^{6,7,8,9} Therefore one has been looking for tests to measure the VOR in the higher frequency range.

A fairly recent development is characterised by both active and passive high-frequency head rotation tests.^{10,11,12,13,14,15} The advantage of these tests is, that no expensive rotatory chair is necessary and results so far have been promising. O'Leary et al. even postulate, that the active Vestibular Autorotation Test (VAT) allows discrimination between an acoustic neuroma and Meniere's disease from a normal ear; also the side and size of the acoustic neuroma might be detected by the VAT.^{16,17} O'Leary et al. studied the VOR during *active* head rotation, using Electro-Oculography (EOG) and a rate sensor on a headband.^{11,13,16,17} They found a gain decreasing in the higher frequency range. We performed a similar experiment, except for using a rate sensor on a biteboard and found a gain staying close to unity over the whole frequency range.¹² In both experiments mentioned above, phaseshift stayed approximately 0°. Tabak et al. were the first to quantify the VOR during high-frequency *passive* head rotation using a specially designed headshaker and measuring eye and head movements by means of magnetic search coils.^{14,15} From 2 Hz on they report a gain of about 1, which decreased

at 8 Hz but then the gain reversed to 1.1-1.3 at 20 Hz. Phaselag increased from zero to about 45° at 20 Hz. Hoshowski et al. found, in experiments with high-frequency whole body rotation, a gain increasing to 1.6 at 4 Hz.¹⁸

In an effort to determine whether the gain of the VOR differs during active versus passive head rotation a direct comparison was made in a group of subjects without any vestibular complaints.

MATERIAL AND METHODS

After informed consent, a total of 14 healthy subjects were studied (age ranging from 24 to 36 years with a mean of 27 years), all of whom had no history of balance, hearing or neurological disorder or neck complaints or optical corrections of visual impairment exceeding 3 diopters. All subjects were instructed not to drink alcohol or take any drugs for at least 24 hours before the test. They were seated and asked to focus on a fixed target of 0.5° on a television screen, 1 meter in front of them. Two experiments were performed on each subject.

Experiment 1; active head rotation.

All 14 subjects were asked to rotate their head smoothly from side to side (yaw) in synchrony with a click, of which the repetition frequency linearly increased from 0.5-6 Hz in 20 seconds. In other studies this method is called the Vestibular Autorotation Test (VAT).^{11,13,16,17}

Experiment 2; passive head rotation.

All 14 subjects were fitted with a helmet containing a computer driven headshaker according to the original idea of Collewyn (Rotterdam, The Netherlands).^{14,15} This is a new technique based on a helmet with torque motor, which oscillates a mass and through that the head. The headshaker enabled passive head rotation from side to side (yaw) with a frequency linearly increasing from 2-6 Hz in 25 seconds.

Head rotation was judged by visual observation of the quality of head movement, optimized by instructing the subjects, and practised by one or more sessions before the actual recording was made. The test was performed three times in each subjects to check reproducibility. Horizontal eye movements were recorded by Electro-Oculography (EOG), with bilateral electrodes positioned on the outer canthi, vertical eye position was recorded with electrodes above and below the right eye; a reference electrode was positioned behind the left ear. Vertical eye position was recorded to detect eye blinking. Angular head velocity was detected by an angular rate sensor (Watsons Ind.) attached to a biteboard.

RESULTS

It often appeared to be impossible for young healthy individuals to reach high rotation frequencies during active head rotations (experiment 1). No subject reached a frequency of 5.5 Hz and only 4 subjects (29%) reached 4.5 Hz. In experiment 2 all subjects reached a rotation frequency of 6 Hz.

Experiment 1, active head rotation.

In Fig 1 mean gain (top), mean phase (bottom) ± 2 SD (standard deviation) are shown; active versus passive head rotation, as a function of frequency. During active head rotation gain was close to unity until 4 Hz and the gain slightly decreased and SD increased. However, only very few subjects reached frequencies over 4 Hz. Phase was invariant during active head rotation at all frequencies, with an average phase lead of 7°. In Table I the numerical data of experiment 1 are shown.

Experiment 2, passive head rotation.

In Fig 1 mean gain (top), mean phase (bottom) ± 2 SD of passive head rotation are shown. During passive head rotation gain decreased from 1.03 at 2 Hz to 0.82 at 6 Hz. Phaseshift was 0° in the whole frequency range. In Table II the numerical data are shown. Coherence was above 0.92 at all frequencies.

Table I. Experiment 1.

Mean gain, mean phase, SD and range of 14 subjects. (only 1 subject reached 5 Hz).

freq	mean gain	SD	range	mean phase	SD	range
2	1.07	0.01	0.92 - 1.18	-5	1	- 5- -24
2.5	1.06	0.01	0.88 - 1.19	-6	1	- 7- -15
3	1.04	0.01	0.88 - 1.25	-7	1	20- -16
3.5	1.03	0.01	0.83 - 1.23	-8	1	-11- -27
4	1.03	0.02	0.88 - 1.19	-7	2	- 4- -22
4.5	0.97	0.08	0.84 - 1.12	-11	2	-6- -16

Figure 1. Gain (top) and phaseshift (bottom) (± 2 SD) related to frequency for active versus passive head rotation.

Table II. Experiment 2.

Mean gain, mean phase, SD and range of 14 subjects.

freq	mean gain	SD	range	mean phase	SD	range
2	1.03	0.01	0.87 - 1.28	-2	1	-22 - -15
2.5	1.03	0.01	0.86 - 1.31	-2	1	-12 - -26
3	1.02	0.01	0.81 - 1.25	1	1	-24 - -15
3.5	0.99	0.02	0.72 - 1.36	2	1	-31 - -13
4	0.97	0.02	0.68 - 1.28	1	1	-26 - -14
4.5	0.94	0.02	0.64 - 1.15	0	1	-14 - -25
5	0.90	0.02	0.65 - 1.12	4	1	-24 - -34
5.5	0.85	0.02	0.58 - 1.05	0	1	-15 - -23
6	0.82	0.02	0.43 - 1.08	-1	1	25 - -15

DISCUSSION

This study was performed to compare the results (gain and phase) of active versus passive head rotation. In a previous study we found that during active head rotation many healthy young individuals were not able to reach high rotation frequencies despite of intensive support and this was confirmed and even more striking in the present study.¹² However, study of the high-frequency VOR is of great impact because most active and passive head movements in everyday activities occur in this range and patients often complain of dizziness in daily life with no disorders found in standard vestibular testing (torsion and calorics). It appeared in this study that during passive rotation, by means of a computer-driven headshaker, all subjects were able to reach a rotation frequency of 6 Hz which allows evaluation of this physiological relevant frequency range.

For detection of head velocity a biteboard was used with an angular rate sensor attached to it, for detection of head velocity. In a previous study we showed that, when using a rate sensor on a headband comparable with O'Leary et al., inaccuracies occurred in detection of head velocity, due to slippage of the headband at high frequencies and by mistake suggest a decrease of gain at higher frequencies.^{13,16,17}

The intraindividual variability was much smaller than the interindividual variability. It was striking, that the gain of some subjects in their 3 passive tests, stayed close to unity at high frequencies, whereas in other subjects the gain decreased at higher frequencies. This distinction between subjects could not be explained and is subject of further investigation.

Goebel et al. studied the VOR during passive and active head rotation at low frequencies up to 1 Hz, using EOG for eye movement detection.¹⁹ At 1 Hz they found no difference in gain (approximately 0.90) during active and passive head rotation. Thus no influence of volition or anticipation on the VOR could be demonstrated at low frequencies using EOG. Collewyn et al. also studied the VOR in active versus passive head rotation at low frequencies up to 1.33 Hz, using magnetic search coils for detection of eye position.²⁶ They found gain values being 3% lower during passive compared to active rotation in the light and 13% in the dark.

During whole body rotation often an increase in gain is reported at higher frequencies. Keller who studied monkeys during passive whole body rotation, found a horizontal gain rising to 1.4 at 4 Hz.²⁰ Benson investigated humans also during passive whole body rotation and found a horizontal gain rising to 2 at 5 Hz.²¹

Analysis of the data in literature suggest that the peak velocity of the stimulus (body or head velocity) does not affect the VOR gain in the velocities applied, which range from 40-200 °/s. So a difference of peak velocity could not explain the differences in gain of the VOR measured upon head or whole body rotation. The increase of gain at higher frequencies has been attributed previously to artefacts due to a poor body and/or head fixation combined with inaccuracies of measuring the effective angular head velocities. However, a recent study, which seem to have overcome these experimental problems, again showed a VOR gain exceeding 1.6 at 4 Hz.¹⁸

So, in the low frequency range upto 1-2 Hz no apparent difference in gain and phase has been reported when comparing active and passive head and whole body rotation. Only Collewyn et al. reported a somewhat smaller gain (reduction of 13% in the dark and 3% in the light) upon passive whole body rotation.²⁶ In the middle frequencies from 2-4 Hz, whole body rotation results in a poor VOR, reflected in gains exceeding 1.3.

Tabak and Collewyn et al. investigated the VOR during passive head rotation up to 20 Hz by means of a computer driven headshaker.^{14,15} Eye and head movements were recorded by magnetic search coils and VOR responses to sinusoidal head movements were analysed. From 2 Hz they found an initial gain of 1, which steadily decreased with a minimum at 8 Hz, and subsequently increased to 1.1-1.3 at 20 Hz. Phase shift increased from about zero to about 45° at 20 Hz.

So, upon active and passive isolated head rotation the VOR is fairly optimal between 2-4 Hz with an almost constant gain of one and approximately no phaseshift. Above 4 Hz active head rotation results in a more optimal reflex as compared to passive rotation: during passive head rotation gain slightly decreases until 0.82 at 6 Hz).

From these results it seems that anticipation might be an important mechanism of optimisation of the VOR gain and phase during active head rotation above 4 Hz. A difference in cervical proprioceptive input (active versus passive) might be another major candidate (see below).

The eye movement strategy may contain a central motor programme. This means, that the VOR could be optimized by the predictability of the target or movements and prior knowledge or experience with the task.^{22,23,24,25,26,27,28,29} However, the finding that there is only a minor difference between active and passive head rotation until 4 Hz, limits the contribution of a central motor programme to the VOR in the frequency range above 4 Hz.

It was described previously that the cervico-ocular-reflex (a possible candidate to account for differences between active and passive head and whole body rotation) is only effective at low stimulus velocities, at low frequencies and in patients suffering from bilateral labyrinthine deficit and is minimal or even completely absent in normal subjects.^{30,31} It has also been suggested, that the additional cervical proprioceptive input could account for the optimisation of the VOR gain during head rotation compared with whole body rotation. The absence of this cervical input during whole body rotation could then be of major importance at frequencies above 2 Hz and could account for an inadequate gain higher than 1.3 (assuming that these experiments were not affected by experimental methodical errors). If the presence of cervical information is a major cause of the better VOR at frequencies above 2 Hz, comparison of whole body rotation and isolated head rotation at higher frequencies might give insight in the cervical contribution to vestibular function. Also, a defective cervical proprioceptive input might affect the gain above 2-4 Hz during passive head rotation.

Analysis of the VOR between 2-6 Hz using EOG in this study results in approximately the same findings (gain and phase) as compared with the scleral coil technique.^{14,15} This would enable and facilitate a broad clinical application of high frequency testing. However, above 4-5 Hz the amplitude of the induced eye velocities is often too small to be detected accurately with EOG.

Conclusions:

- Whole body rotation shows a poor VOR at about 4 Hz in contrast to head rotation. This is probably due to the lack of cervical proprioception.
- Active head rotation limits objectivation of the VOR to 4 Hz.
- The VOR shows similar characteristics up to 4 Hz for both active and passive head rotation.
- Above 4 Hz anticipation seems to be the major cause for the optimal VOR during active rotation versus passive head rotation.
- The high-frequency VOR can be measured accurately by EOG up to 4-5 Hz.

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Chapter

4

**The vestibulo-ocular reflex during
passive high-frequency head rotation
in Meniere's disease**

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Submitted.

ABSTRACT

Confirming the diagnosis of Meniere's disease (MD) in terms of quantifying vestibular function loss is difficult because to our knowledge an absolute discriminating diagnostic test does not exist. We evaluated the clinical usefulness of the passive high-frequency test to objectify vestibular function loss in MD patients. 20 Patients were tested, all reaching frequencies up to 6 Hz without difficulty. Above 3 Hz a significant larger phaselag was found in MD patients compared to normal subjects. An interesting finding in this study was that 4 MD patients, with normal caloric responses and a normal low-frequency Vestibulo-Ocular Reflex (VOR), had an abnormal high-frequency VOR during passive head rotation. Between 3 and 4 Hz the discriminative power of the high-frequency test using Electro-Oculography (EOG) (MD patients versus normal subjects) is maximum. Only 2 out of 20 patients fell into the normal range of gain and phase, however these patients showed abnormal caloric responses. At 5 and 6 Hz the predictive value of the test is less accurate probably due to an increasing noise contribution to the signal using EOG.

INTRODUCTION

Meniere's disease is generally considered as an inner ear disorder resulting in the classical triad of symptoms of attacks of vertigo, unilateral sensorineural hearing loss and tinnitus. There appears to be a great variability of the outcome of the two most frequently applied vestibular function tests in MD patients. As many as 30-50% of these patients show normal responses to caloric stimulation.^{1,2} In some studies normal caloric responses and abnormal rotational chair test results are reported, or vice versa.^{3,4} The poor correlation between complaints and test outcome might have been the major argument not to use the outcome of these low-frequency vestibular function tests for classification of MD according to the AAO-HNS criteria.⁵ The conventional test battery seldom includes assessment of the VOR during high-frequency rotation, because of technical limitations of most rotational chair systems and because of problems concerning head and body stabilisation. However, it becomes increasingly more clear that tests evaluating the vestibular function at high frequencies might be more reproducible and more sensitive.^{6,7,8,9} High-frequency vestibular testing indeed evaluates the VOR in the more physiological frequency range, because natural active and passive head movements such as during walking contain frequencies up to and even exceeding 8 Hz.^{10,11} Another advantage is that above 2 Hz no smooth pursuit activity is present, minimising visual interaction with the vestibular response and reducing the impact of the mental instruction set upon the responses.¹² Below 2 Hz, the contribution of the VOR to visual stabilisation can be strongly influenced or even suppressed by the visual system and/or cognitive processes such as imagined visual targets.^{13,14}

Recently passive and active high-frequency head rotation tests have been introduced as a clinical diagnostic tool.^{15,16,17} The active test, the so called Vestibular Autorotation Test (VAT) has proved to be of diagnostic value in MD patients.^{18,19,20} In our hands the test was limited by the fact that most people were not able to actively reach high rotation frequencies and the reproducibility of the test was considered not sufficient.¹⁷ Therefore we recently measured the VOR using *passive* high-frequency head rotation in normal subjects by use of a computer controlled headshaker which allowed quantification of the VOR from 2-6 Hz.²¹ The purpose of this study was to evaluate the VOR, during passive high-frequency horizontal (yaw) head rotation, in MD patients.

MATERIAL AND METHODS

Patients population.

After informed consent, twenty MD patients, as established by the AAO-HNS criteria were included in the study.⁵ Excluded were patients with a history of neurological disease, signs of oculomotor dysfunction or neck complaints.

All patients included, 14 females and 6 males, were disabled by the disease and hardly or not responding to conservative treatment. The age ranged from 40 to 72 years, with an average of 53 years. The duration of the disease ranged from 1 to 14 years, with an average of 5 years. All patients had had several classical attacks of vertigo and most of them were unsteady most of the time. Based upon the audiological findings and the complaints 11 patients were judged to suffer from the disease by function loss of the left ear, 5 by function loss of the right ear and 4 of both ears. All patients underwent a general vestibular examination. No abnormalities were observed upon the oculomotor tests (saccades, pursuit, optokinetics). In all patients the multi-frequency torsion swing test (0.02 - 0.32 Hz) showed a normal gain, phase and coherence and no pathological nystagmus or eye velocity preponderance was found. The caloric test showed normal responses in 4 patients and an ipsilateral hyporeflexia in 16 patients (less than 10°/s on both the cold as well as the warm irrigation) with a unilateral weakness ranging from 21 to 97 %. Pathological nystagmus preponderance was not observed.

Experiment

In order to assess the VOR each patient was asked to sit on a chair and fixate a stationary target (diameter 0.5°, 530 nm) at a distance of 1 meter. During fixation the head of the patient was rotated horizontally (yaw) by a computer driven headshaker, according to the original idea of Collewyn.^{6,7} The sinusoidal rotation frequency increased from 2-6 Hz in intervals of 1 Hz, each lasting 10 seconds. Every patient was tested three times during one session. Eye movements were recorded by EOG. Head velocity was measured by a calibrated angular rate sensor on a biteboard (Watson Ind). Horizontal and vertical EOG leads as well as the angular rate sensor output were fed into a Toennies Nystagliner system for data storage and analysis. Analysis of the data is described in detail elsewhere.^{17,22} The VOR was quantified by three parameters extracted from the spectral analysis : gain, phase and coherence. VOR gain was defined as the ratio of eye velocity and head velocity. VOR phase was defined as the phaselag or phaselead of eye velocity relative to head velocity expressed in degrees relative to 180 degrees. A negative value was defined as phaselag and a positive value was defined as phaselead. The coherence was calculated to verify the validity of each gain and phaseshift value obtained. For each patient the results of the three tests (gain, phase and coherence) were averaged. Statistical analysis was performed using

commercial available statistical software SPSS PC version 4.0. Analysis involved calculation of group averages and standard deviations of individual values (T-tests, ANOVA).

RESULTS

All patients reached rotation frequencies up to 6 Hz without difficulty. In general we observed that the reproducibility and coherence decreased above 4 Hz due to a decrease in the signal-to-noise ratio and an increase of non-harmonics. Table I shows the mean gain, phaseshift values and standard deviation (SD) for all frequencies and in Fig 1 these values are visualised and compared with normative data as established previously.²¹ At 2 Hz no significant difference in gain and phase values could be obtained in MD patients compared to normal subjects. At higher frequencies MD patients tended to a lower gain (but statistically not significant) and a significantly increased phaselag (T-test, $p < 0.05$). It is shown that at 3 and 4 Hz the difference between normal subjects and patients is maximal. Only 2 out of 20 patients fell into the normal range (± 2 SD) of gain and phase (both patients were earlier found to be characterised by unilateral caloric hyporeflexia). All other 18 patients, including those 4 patients with normal calorics and normal low-frequency torsion VOR, had gain and phase values differing more than 2 SD from the average values of the normal population. In all patients and tests coherence values were above 0.94. Standard deviations in normal subjects were found to be smaller than in patients, especially concerning phaseshift values. Interindividual variability was greater than intraindividual variability. A larger variability in patients compared to that in normal subjects has also been reported by O'Leary et al.^{18,19}

Figure 1. Gain (top) and phaseshift (bottom) (± 2 SD) related to frequency of Meniere's disease patients versus normal subjects.²¹

The VOR during passive high-frequency head rotation in Meniere's disease

Table 1. Mean gain, mean phase, SD and range in patients with Meniere's disease.

freq	mean gain	SD	range	mean phase	SD	range
2	1.08	0.02	0.83 - 1.19	-1	1	-18-18
2.5	1.05	0.02	0.81 - 1.16	-3	2	-23- 13
3	1.02	0.02	0.81 - 1.18	-6	2	-37-16
3.5	0.98	0.02	0.71 - 1.23	-7	3	-25- 3
4	0.93	0.02	0.68 - 1.13	-8	3	-36- 16
4.5	0.90	0.03	0.62 - 1.20	-8	4	-25- 14
5	0.86	0.03	0.61 - 1.10	-8	4	-38- 24
5.5	0.82	0.03	0.55 - 1.08	-10	5	-27- 28
6	0.77	0.03	0.44 - 1.03	-11	5	-57-19

DISCUSSION

An increasing phaselag of the VOR in higher frequencies was suggested to be a useful general diagnostic indicator for MD patients by Matthew et al. using the so called high-frequency Vestibular Autorotation Test (VAT).¹⁹ They found no difference between patients suffering from MD in the acute stage of the disease and normal subjects. However, in the chronic stage of the disease decreased gain values and increasing phaselags in the higher frequencies were found. At 5 and 6 Hz 85% of the MD patients were found to have "abnormal" gain or phase values regardless the clinical stage. However, it must be stressed that Matthew et al. defined the normal range by the average ± 1 SD, which is statistically considered not significant.¹⁹ If the more accepted criterium of ± 2 SD is applied less than half of the patients show abnormal values.

O'Leary & Davis reported an increased velocity gain at high frequencies during active vertical head rotation from 2-6 Hz in 10 patients in the acute stage of MD.¹⁸ However, in a pilot study performed in normal subjects we were unable to obtain reproducible results in case of active vertical head rotation due to the poor linearity and reliability of the vertical leads applying EOG. Compared to horizontal rotation, it was even more difficult to reach high rotation frequencies during vertical rotation and more eye blinking artefacts occurred.

In summary: literature shows that the VOR observed in high-frequency *active*

horizontal *head* rotation seems not to be affected in MD patients.

Dayal & Tomlinson used *pseudorandom whole body* rotation of 2-5 Hz comparing normal subjects and MD patients. In the higher frequency range patients showed a gain exceeding normal values.²⁰ This increased gain was attributed to the acceleration sensitivity of the semicircular canal afferents at high frequencies. Phase values were not discussed. However, these results should be interpreted with caution because inaccuracies in body and head fixation as well as head velocity detection often occur in case of high-frequency whole body rotation.²³ Nevertheless, pseudorandom stimulation is preferred above sinusoidal stimulation, because it excludes optimisation of the VOR by prediction and anticipation. Unfortunately, we were forced to apply predictive sinusoidal stimuli, because from a pilot study we found that the gain, phase and coherence of the VOR using pseudorandom passive high-frequency head rotation could not be detected with sufficient reproducibility. The major problems appeared to be *i.* the poor transfer of the stimulus upon the head (limitation of helmet to head coupling) which induced irregular stimulus patterns and *ii.* the artefacts induced by the motor (induction and the electrode movements) upon the EOG registration. Pure sinusoidal stimulation allowed sufficient filtering and frequency specific analysis for artefact rejection and improvement of the signal-to-noise ratio.

In this study the response upon *passive* head rotation (2-6 Hz) using a computer driven headshaker in 20 MD patients could be evaluated reproducibly, without any difficulty and without causing dizziness. Compared to normal subjects in MD patients the VOR gain did not change significantly between 2-6 Hz (Fig 1). In contrast to the experiments described above concerning active head rotation, above 3 Hz the phaselag in patients was significantly larger than in normal subjects (Fig 1). Four patients, clinically defined as having MD according to the AAO-HNS criteria⁵, with normal calorics and a normal low-frequency VOR, had abnormal gain and phase values during passive head rotation, which might indicate the relevance of evaluating the high-frequency VOR. At 3 and 4 Hz the difference between normal subjects and patients is maximum). Above 4 Hz the accuracy of the measurements decreased (non-harmonics, decreased signal-to-noise ratio) which reduces the ability to discriminate between normal subjects and patients. The relative large number of patients with an abnormal test result of their passive high-frequency test (18 out of 20) may indicate that the population under survey suffered from a severe stage of MD. This interpretation is supported by the finding that 16 out of 20 patients (80%) showed abnormal caloric responses where a prevalence of 50-70% has been reported in literature.^{1,2} The results of Matthew et al. show a tendency that the high-frequency VOR deteriorates in the chronic stage of the disease.¹⁹ Quantification of low- (calorics) and high- (head rotation) frequency testing

in a longitudinal study of MD patients might inform us about the relation between test outcome and disease stage or severity.

The discrepancy between the results obtained by passive (increased phase lag in MD patients) versus active (no significant effect) head rotation could be explained if one assumes that the anticipation and active control are able to compensate for the high-frequency function loss. This assumption is supported by our previous finding that in normal subjects the VOR is better (gain is 1, phaselag is 0) during active head rotation compared to passive head rotation.^{17,21} Anticipation and maybe a central motor programme are supposed to account for better gain and phase results during high-frequency active head rotation compared to passive rotation in normal subjects. It is suggested that also in MD patients this contribution is still able to compensate for vestibular loss and achieve good gain and phase results during active head rotation and that the function loss can only be detected by use of non-voluntary stimuli. The observation that unpredictable high-velocity impulses are also useful in detection of 'low-frequency compensated' vestibular lesions supports this interpretation.^{6,7}

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Chapter

5

**The vestibulo-ocular reflex during
passive high-frequency head rotation
in patients with
bilateral vestibular impairment**

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Accepted for publication in Otolaryngology Head and Neck Surgery

ABSTRACT

Several tests have been proposed to quantify the residual function in patients with bilateral loss. The total sum of responses to the four standard caloric irrigations has been put forward as an useful measure. It has been shown however, that even in case of a complete caloric areflexia, a Vestibulo-Ocular Reflex (VOR) can still be induced by angular accelerations using rotatory chairs. We studied 8 patients with bilateral absent or reduced caloric responses, using a passive headrotation test to assess the high-frequency VOR. The question was, whether a substantial VOR could be induced by high-frequency head rotation and if so does this reveal the functional status of the patients better than the outcome of the caloric test and low-frequency whole body rotation (torsion swing). All patients, even those with a complete caloric or torsion swing areflexia, showed a substantial VOR at frequencies above 2 Hz, although with a reduced gain above 4 Hz compared to normal subjects. The large inter-subject variation of both the dependent and the independent variables hinders a clear interpretation of the data. Therefore, despite the small sample, we calculated the Spearman correlation coefficients between the variables and performed a discriminant analysis in order to gain more insight in the data. This analysis showed that a linear combination of the gain of the torsion swing (low-frequency) and the gain at 4.5 Hz could predict group membership based on clinical symptoms. Results of caloric testing had no additional value. These results have to be read with precaution because of the small number of patients with function loss with a variety of etiologies.

INTRODUCTION

From clinical observations it is well known that patients show a remarkable ability to compensate for loss of peripheral vestibular sensitivity.^{1,2} Compensation for a bilateral vestibular impairment requires more time and is less complete than compensation for a unilateral lesion, but even these patients often return to near normal activity. Quantification of the residual vestibular function in patients with bilateral impairment is difficult because the accuracy of vestibular tests is especially poor at low response levels. Several tests have been proposed to quantify the residual function in patients with bilateral loss. The total sum of responses to the four standard caloric irrigations has been put forward as a useful measure.³ Higher response levels can even be obtained by increasing the stimulus intensity as is done by application of ice-water instead of water of 30° or 44° Celsius. However, this technique appears to lack sensitivity and should only be used to determine whether there is any vestigial VOR left at all and not as a quantitative measure.⁴ Also, it has been shown that even in case of a complete caloric areflexia, a VOR can still be induced by angular accelerations using rotatory chairs.^{5,6} Several aspects might account for the higher sensitivity of rotatory tests as compared to the caloric test. First, in case of rotatory tests the two labyrinths are stimulated simultaneously, whereas during the caloric test only one labyrinth is stimulated per irrigation. Second, the gain of the VOR depends on the stimulus frequency due to the mechanical properties of the semicircular canal system.⁷ The reflex is optimal between 1 to 8 Hz and decreases rapidly outside this range.^{8,9,10} Caloric irrigation can be considered as equivalent with a 0.003 Hz, inefficient low-frequency stimulus.¹¹ The stimulus applied in standard rotatory tests ranges from 0.01 to 0.5 Hz, which is closer to the optimal frequency range (1-10 Hz). It can be expected that frequencies above 0.5 Hz are even more effective in showing the residual vestibular function.

In succession of our previous studies of the high-frequency VOR we studied 8 patients with a bilateral absent or reduced caloric response.^{12,13} The VOR characteristics of these patients were assessed by a passive high-frequency head rotation test. The following questions were addressed: *i.* can a substantial VOR be induced by high-frequency rotatory stimulation in patients with bilateral caloric hypo- or areflexia? and if so *ii.* does the gain and phaseshift of the high-frequency VOR reveal the functional status of the patients better than the outcome of the caloric test and low-frequency whole body rotation?

MATERIAL AND METHODS

Patients population.

Table I shows the signs and symptoms of 8 patients, 5 females and 3 males, included in this study. In 4 patients (50%) the cause of the vestibular impairment was unknown. The history and symptoms of the other four patients did point to a diagnosis. Patient RB was known with epilepsy for many years, but since 5 years also suffered from vestibular symptoms, sensory-neural hearing loss and tinnitus, which together with the abnormal findings during vestibular testing (Table I) pointed to Meniere's disease. Patient ME experienced vestibular symptoms after a steel bar fell on her head and she showed post-traumatic a reduced caloric response, suggesting a labyrinth trauma which could not be confirmed by radiology. Patient WW experienced vertigo, unsteadiness, oscillopsia after a whiplash injury (quite exceptional in our laboratory) and showed a caloric areflexia. Pretraumatic data were not available. Patient W was known with a congenital deaf left ear. Considering all data a labyrinth trauma of the right ear together with a congenital deficit of the left ear were assumed to be the most likely cause of the areflexia. Patient EN suffered from acute vertigo, at the long term followed by unsteadiness and oscillopsia. Electro-Oculography (EOG) showed no responses on the caloric or low-frequency rotatory test. Immunological examination pointed to autoimmune disease (polyarteritis nodosa) as the primary cause of function loss.

All patients underwent a general vestibular examination. No abnormalities were observed upon the oculomotor tests (saccades, pursuit, optokinetics). This was also observed in patient RB who used anti-epileptic medication (Tegretol).

In all patients a low-frequency pseudorandom whole body rotation test (0.02-0.32 Hz) was performed (Table I). All had absent or reduced caloric response on standard bithermal caloric testing (sum of the peak slow phase velocity after each stimulus divided by 4 less than 5°/s).¹⁴ None of the patients had a pathological spontaneous nystagmus while fixating: if any spontaneous nystagmus was present with eyes open in the dark the average slow phase velocity did not exceed 3°/s.

The VOR during passive head rotation in bilateral vestibular impairment

Table 1. Data of 8 patients with bilateral reduced caloric responses. The caloric response is expressed in °/s (maximal slow phase velocity); L=left, R=right, W=warm 44° C=cold 30 °C. Symptoms were characterised by a number: 0= not disabled, 1= slightly disabled, 2= moderately disabled, 3= severely disabled.

Initials	Diagnosis	Age	Years since onset	Current symptoms	Calorics	Low-freq whole body rotation
EN	autoimmune disease	31	5	oscillopsia 1	RW:0,LW:0 RC:0,LC:0	no VOR
HV	unknown	46	4	not disabled 0	RW:0,LW:9 RC:3,LC:4	normal
DS	unknown	54	6	unsteady, attacks of vertigo 3	RW:0,LW:6 RC:4,LC:3	no VOR
RB	central? (epilepsia)	54	5	oscillopsia, attacks of vertigo, stopped cycling and driving 3	RW:5,LW:5 RC:5,LC:4	no VOR
IR	unknown	24	3	unsteady and nauseated 3	RW:0,LW:0 RC:0,LC:0	no VOR
MD	unknown	71	6	oscillopsia and sometimes attacks of vertigo 2	RW:5,LW:6 RC:5,LC:3	VOR gain nearly normal
ME	trauma?	51	2	even gives aerobic lessons 0	RW:3,LW:4 RC:4,LC:2	normal
WW	congenital? trauma?	46	4	always unsteady, oscillopsia, no cycling anymore 3	RW:0,LW:0 RC:0,LC:0	no VOR

Experiment

In order to assess the VOR each patient was asked to sit on a chair and fixate a stationary target (diameter 0.5°, 530 nm) at a distance of 1 meter. During fixation the head of the patient was rotated horizontally (yaw) by a computer driven headshaker, according to the original idea of Collewyn.^{8,9} The sinusoidal rotation frequency increased from 2-6 Hz in intervals of 1 Hz, each lasting 10 seconds. Eye movements were recorded by EOG. Head velocity was measured by a calibrated angular rate sensor

recorded by EOG. Head velocity was measured by a calibrated angular rate sensor mounted on a biteboard (Watson Ind). Horizontal and vertical EOG leads as well as the angular rate sensor output were fed into a Toennies Nystagliner system for data storage and analysis. Analysis of the data is described in detail elsewhere.^{10,12,15} The VOR was quantified by three parameters extracted from the spectral analysis: gain, phase and coherence. VOR gain was defined as the ratio of eye velocity and head velocity. VOR phase was defined as the phaselag or phaselead of eye velocity relative to head velocity expressed in degrees relative to 180 degrees. A negative value was defined as phaselag and positive value was defined as phaselead. The coherence was calculated to verify the validity of each gain and phaseshift value obtained; a test was only accepted if coherence at all frequencies exceeded 0.93. Every patient was tested three times during one session. For each patient the results (gain, phase and coherence) of the three tests were averaged. The large inter-subject variation of both the dependent and the independent variables hinders a clear interpretation of the data. Therefore, despite the small sample, we calculated the Spearman correlation coefficients between the variables and performed a discriminant analysis in order to gain more insight in the data using commercially available software (SPSS-PC version 6.1.2).

RESULTS

All patients reached rotation frequencies up to 6 Hz without difficulty. In general we observed that the reproducibility decreased above 4 Hz due to a decrease in the signal to noise ratio and an increase of non-linearities.

Fig 1 and 2 show gain and phase values respectively of each individual patient related to frequency. Only individual data are shown, as etiology of the function loss and vestibular test outcome varied too much to justify averaging. However, all patients showed a reduced gain above 4-5 Hz as compared to normal individuals.¹² In patients RB, MD, IR the gain was already reduced above 3.5 Hz, whereas the gain in patients EN and WW was decreased already at low frequencies. In patient EN VOR gain surprisingly increased again above 4.5 Hz up to normal values at 6 Hz.

Patients DS, HV, MD and IR showed normal phaseshifts, whereas patients RB, WW and EN showed a considerable abnormal phaselag, while patient ME showed an abnormal phaselead. These phenomena appeared to be reproducible over the three consecutive tests performed in each patient. In order to allow a correlation and discriminant analysis, symptoms were classified (see Table I). The correlation analysis showed that symptoms were linearly correlated with the outcome of the torsion swing test ($r=0.84$, $p=0.009$). Regarding outcome of the high-frequency test the gain

correlations were found, irrespective exponential, logarithmic or quadratic transformation. Discriminant analysis showed that the outcome of the low-frequency test alone could predict group membership based upon symptoms with a correct classification of 75%. A linear combination of the gain at 4.5 Hz and the low-frequency gain resulted in a correct classification of 87.5 %. Results of caloric testing had no additional value apart from detecting the side of the lesion.

Figure 1. Passive head rotation in patients with bilateral vestibular impairment. Gain related to frequency for each patient.

Figure 2. Passive head rotation in patients with bilateral vestibular impairment. Phaseshift related to frequency for each patient.

DISCUSSION

From literature it is known that patients with a bilateral caloric hyporeflexia often show substantial or even normal VOR at low-frequency torsional stimulation.^{5,6,16} Interestingly, in this study all patients showed a high-frequency VOR gain clearly different, but not absent, from that observed in normal subjects. The high-frequency VOR phaseshift was abnormal in four out of the total of eight patients. The high-frequency VOR correlates better with the caloric response than the low-frequency rotation test. The latter appears to be the only test correlated with the functional status of the patient: an absence of low-frequency VOR implies in 4 out of 5 cases disability. Four patients were not really disabled (EN, HV, MD, ME). Three of these four (HV, MD, ME) had near normal or normal low-frequency and only slightly abnormal high-frequency responses. Apparently, slightly abnormal high-frequency responses alone, do not imply a low level of disability (DS, IR), whereas disability seems to be correlated with the impairment of *both* low- and high-frequency VOR. The results in Patient EN were remarkable and exceptional: absent low-frequency and abnormal high-frequency responses and hardly any symptoms.

Total absence of caloric response in our study was related with the absence of the VOR during low-frequency whole body rotation (Table I; patient EN, IR, WW), which might be an accidental finding.^{5,6} Patients with an absent VOR during low-frequency rotation had a tendency to show lower gains in higher frequencies.

After bilateral vestibular function loss, most patients return to near normal lifestyle, but when high-skilled locomotor performances are demanded, neither man nor animal can compensate completely for this vestibular loss. Most labyrinthine defective individuals experience imbalance and a disturbing illusion of movement of the environment while walking or moving the head rapidly (oscillopsia).^{17,18} This transient blurring of vision during rapid head movements is a very common, but not compulsory finding, as was also reported by patients in this study.¹⁹ One would expect that patients who experience oscillopsia would have more difficulty performing in high-frequency rotation tests. This could not be confirmed in this study, maybe also because some patients were unable to describe their subjective sensations precisely.

Patients with bilateral vestibular loss are often well-compensated in every-day life situations, which can be attributed to the development of a number of compensatory mechanisms which take over the stabilising role of the slow-component VOR.^{20,21} One of these mechanisms is supposed to be the Cervico-Ocular Reflex (COR). The existence of a COR in man has been recognised since Bárány's early observations but its function remains a matter of controversy.²² The COR, although virtually non-

existent in normal monkeys, has been shown in labyrinthectomised monkeys to become increasingly instrumental in restoring the slow compensatory eye movements which accompany head movements.²¹ In literature a large variability in gain of the COR is reported, not only among normal subjects but also in patients with bilateral vestibular loss. The results of studies of the neck-eye reflexes in humans with absent vestibular function are by no means as clear cut as in animals.^{20,23,24,25,26,27} The influence of the COR is considered to be small during high frequencies, low velocities and passive head movements.^{21,28,29,30} Therefore we assume that the COR does not substantially contribute to the gaze stabilisation at high-frequency passive head rotation in normal subjects. It is possible, that in our patients with bilateral vestibular impairment, the COR contributes to the ocular responses to some extent, especially in the lower frequencies. Huygen et al. investigated 30 patients and found that the COR-gain was frequency dependent, decreasing from 0,7 at 0,1 Hz to 0,4 at 0,4 Hz.²⁶ Therefore it is unlikely that the COR contributes to a great extent to the ocular responses found in our patients with bilateral vestibular impairment at the higher frequencies.

High-frequency vestibular tests using head rotation in patients with bilateral vestibular impairment has not been performed to a great extent yet. Hydén et al. studied the VOR during high-frequency whole body rotation.³¹ At high frequencies (>3 Hz) all patients showed reduced VOR gains compared to normal subjects. At low frequencies gain values were close to normal when using a predictable stimulus (sinusoidal). With a non-predictable (pseudorandom) stimulation gain values were significantly reduced even at lower frequencies. Patients with the most severe loss showed a phaselag at higher frequencies. It must be stated that gains were found to increase at higher frequencies, possibly due to an artefact in detecting head velocity.

Tabak et al. studied 3 patients with bilateral vestibular impairment also using passive high-frequency head rotation using magnetic search coils for detection of eye and head position.^{8,9} Values of the VOR gain for these patients were clearly lower and phaselags larger, compared to normal subjects in the 2-8 frequency range. The patient who had only mild vestibular symptoms in daily life, showed better VOR gain and phase values. They concluded that this might indicate that high-frequency VOR characteristics correlate well with function, compensation and clinical recovery after bilateral vestibular impairment. This relationship of high-frequency gain and clinical recovery could only be partly confirmed in our study: patients with the best gains in the highest frequencies were less disabled by the disease. The relationship with phaselag was not as clear.

In conclusion: First, a substantial VOR can be induced by high-frequency rotatory stimulation in patients with bilateral caloric hyporeflexia, which suggests a residual

vestibular function. Second, discriminant analysis showed (although this should be read with some precaution because of the small sample) that a linear combination of the gain at 4.5 Hz and the average low-frequency gain (torsion swing 0.02-0.32 Hz) could predict group membership based upon symptoms with a correct classification of 87.5 %. Results of caloric testing did not improve group recognition.

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Chapter

6

**The passive high-frequency
head rotation test as a tool
to quantify the effect of betahistine**

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*This study has been accepted for publication in a slightly revised version in the Acta
Otolaryngol (Stockh).*

ABSTRACT

The effect of betahistine on the Vestibulo-Ocular Reflex (VOR) was assessed in twelve patients suffering from paroxysmal vertigo. Only patients who responded beneficial to betahistine treatment were admitted to the study in order to increase the probability of quantifying the effect of the drug on vestibular function. Patients received placebo or 16, 32 or 64 mg betahistine orally under double-blind conditions. Vestibular function was tested a few minutes before intake, and 1,2,3,4,6, and 8 hours after intake, by torsion swing stimulus in the dark and by high-frequency passive head rotation in the light. Betahistine significantly affected the velocity gain of low- and high-frequency VOR. The reduction in gain was maximal about 4 hours after administration of the 16 mg dose in the torsion swing experiment and the 32 mg dose in the head rotation experiment. Above these doses, the effect on velocity gain was less marked. These results suggest that betahistine has a complex action on H_1 - H_3 receptors and that the site of action may be in the vestibular nuclei.

INTRODUCTION

Although its precise mode of action is still subject of investigation, betahistine dihydrochloride has been extensively studied and applied in the treatment of vertigo.^{1,2,3,4,5} It appears to antagonize the H_3 -autoreceptor located on histaminergic nerve cells, where it is a more effective antagonist than histamine.^{4,5} In contrast, the agonistic activity of betahistine on H_1 and H_2 receptors is less marked than that of histamine. Histamine inhibits its own release via this autoreceptor (negative feed back), a process which can be antagonized by betahistine resulting in facilitation of histaminergic neurotransmission in the brain. Thus, betahistine appears to be a weak H_1 agonist causing release of Ca^{++} , a weak H_2 agonist causing synthesis of cyclic AMP and a strong H_3 antagonist causing release of histamine. The action of betahistine on the H_3 receptor might explain why relatively low concentrations can effectively modify neurotransmission in the brain by decoupling the negative feedback loop controlling histamine release.^{4,5}

In animals, betahistine increases intra-labyrinthine blood flow and oxygenation of sensory tissue and causes a dose-dependent inhibition of polysynaptic neurons in the lateral vestibular nuclei.^{1,2,3} Recently, betahistine has been shown to hasten central compensation after labyrinthectomy in cats, a process which is thought to be controlled by cerebellum and vestibular nuclei.⁶ It is also interesting to note that nystagmus activity seems to be reduced by betahistine in humans.⁷

Although the majority of placebo-controlled, double-blind studies show that betahistine is effective in the treatment of vertigo, this is not a universal finding.^{7,8,9,10,11,12,13,14,15} The same holds true for the inhibitory effect of betahistine on nystagmus induced by vestibular stimulation.^{7,11} Thus, although the balance of the current evidence suggests that betahistine reduces vertigo and vestibular induced nystagmus activity, there is a clear need for more detailed research to explain the differences in the outcome of different studies and to gain further insight into its mode of action and indications.

Two major problems complicate the objective assessment of any anti-vertigo therapy. Firstly, VOR measurements in the dark (caloric and rotational tests) suffer from poor reproducibility and are strongly influenced by the instructions given to the subjects and their state of alertness. VOR in the dark is markedly influenced by subjective factors and gain can be changed, at will, from 0.35 to 0.95 by imagining respectively a visual target which either moves or is fixed.^{16,17,18,19,20,21} Moreover, VOR-gain recalibration occurs within minutes. As a consequence, system parameters, which are well defined when a visual target is present, may be less reliable when testing is done in the dark. In general, this precludes the measurement of small drug effects; sufficient discrimination is only available by numerous repeated tests or from group averages on extended

sample sizes. Secondly, classification of patients based on their history and a general and vestibular examination remains imprecise. The effects of betahistine on nystagmus and vertigo have been studied predominantly in patients presumed to be suffering from peripheral vestibular (labyrinthine) disorders. However, the available diagnostic tools (history, general clinical examination, audiology and other advanced vestibular examination, and radiodiagnostics) seldom permit a high degree of certainty in the etiological classification of labyrinthine disorders. Indeed, peripheral vestibular disorder is often a diagnosis of exclusion following failure to demonstrate a convincing central etiology. No generally accepted vestibular test exists to discriminate between labyrinthine and vestibular nerve lesions; although the galvanic stimulation test has been proposed for this application, it retains some fundamental disadvantages. These diagnostic difficulties lead to poorly defined patient groups. Thus, a population with the same clinical diagnoses may be composed of subjects with a variety of diseases with different etiologies. As the effectiveness of a therapy is dependent upon the etiology of the disease, the mean outcome will depend on the random composition of the population selected for the study.

In order to study and quantify the effect of betahistine on vestibular function whilst overcoming these problems, only patients who suffered from paroxysmal vertigo and who indicated that their complaints markedly reduced by betahistine (3x16 mg per day) were included. Selecting a population of patients who had responded clinically to betahistine should reduce the etiological heterogeneity of the sample and allow the effects of betahistine on vestibular function to be more readily demonstrated.

MATERIAL AND METHODS

Patient population

Twelve patients (age 18-50 years) suffering from paroxysmal vertigo (defined as an illusion of rotation, either of the patient or surroundings), of which both frequency and intensity of the vertigo had been reduced by betahistine (16 mg 3 times per day) according to the patient's judgement, were enrolled in this double-blind, randomised, placebo-controlled, multiple dose study.

Vertigo must have been present for at least 3 months, with attacks occurring at least twice a month prior to the use of betahistine. Betahistine medication was interrupted 1 week before the start of the study. Patients were excluded if they were pregnant, lactating or of childbearing potential and not taking adequate contraceptive measures, or if they had a history of allergies, hypertension, diabetes, pheochromocytoma, peptic ulcer, asthma, drug or alcohol abuse or hepatic, renal or cardiovascular disease. Other exclusion criteria included a history of aspecific dizziness, benign paroxysmal positional dizziness (BPPD), neurological or psychological disorders, hearing disorders, abnormal pure tone audiometry, trauma of the ear, earinfection or eye disorders

affecting the extra-ocular musculature, impaired monocular vision (<0.8), congenital or acquired fixation nystagmus, impaired smooth pursuit or optokinetic reflexes, or total impairment of the torsion swing test; contact lenses.

Patients were not permitted to receive any medication in the week prior to, during the study with the exception of oral contraceptives and mild analgesics (eg. aspirin, paracetamol). Flunarizine was not permitted in 7 months prior to the study. Alcohol and coffee (or other caffeine-containing drinks) were not permitted during the study sessions; alcohol was also not permitted in the 24 hours before each session and coffee (or other caffeine containing drinks) in the 12 hours before each session.

All patients provided written informed consent. The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki.

Study design

The study was conducted according to a double-blind placebo-controlled, Latin square design. Four single oral dosages (16, 32 or 64 mg betahistine or placebo) were allocated randomly so that each dosage was initially received by three patients; each patient underwent four sessions, each lasting 8 hours, during which they were oscillated on a torsion swing test (experiment 1) and the head was oscillated using a computer-driven head rotating device (experiment 2).

Each test was performed immediately prior to drug intake and 1, 2, 3, 4, 6 and 8 hours after drug intake. The baseline recordings were performed after a light breakfast and the study drug was then taken with 250 ml of water. A light lunch was provided 5 hours after drug intake. Patients were permitted a glass of mineral water or orange juice after each test. Smoking was kept to a minimum during the sessions. The interval between each of the four sessions with different dosages was more than one week but did not exceed two weeks.

Test procedures

Experiment 1: low-frequency whole body rotation in the dark

In order to provide a comparison with other studies, the patient was rotated sinusoidally in complete darkness, with eyes open, on a computer-driven rotary chair (Toennies Pro, Wuerzburg) for 160 seconds at a maximum velocity of 50°/s (10 cycles, 0.0625 Hz).⁷ The subject was kept alert by performing a calculation task and communicating with the investigator during rotation. Head angular velocity (which correlates body velocity at these low-frequencies) was recorded by a tachometer mounted at the axis of the rotatory chair.

Experiment 2: high-frequency passive head rotation

A fairly recent development as an alternative to a rotation test in the dark is the passive high-frequency head rotation tests in the light.^{22,23,24} For this purpose, patients were

fitted with a helmet containing a computer-driven "headshaker" as described by Taba and Collewyn.²³ This new technique is based on a helmet containing a torque motor which oscillates the head. With this "headshaker" it was possible to passively rotate the patient's head from side to side (yaw) with a linearly increasing frequency from 1 to 6 Hz over a period of 30 seconds. Patients were asked to fix a visual target as well as possible throughout the test. This high-frequency test was performed in the light (10 Lux incident on the head) as the signal-to-noise ratio in electro-oculography (EOG) is much better under these conditions and, at high frequencies, no difference appears to exist between testing in light and testing in darkness. Gain, phase and coherence were calculated after removal of saccades and eye blinks by median filtering.²⁵ Angular head velocity was recorded by an angular rate sensor (Watsons Ind.) attached to the biteboard.

During head rotation possible influence of the neck should be considered. The existence of a Cervico-Ocular Reflex (COR) in man has been recognised since Bárány's early observations but its function remains a matter of controversy.²⁶ The COR, although virtually non-existent in normal monkeys, has been shown in labyrinthectomised monkeys to become increasingly instrumental in restoring the slow compensatory eye movements which accompany head movements.²⁷ The results of studies of the neck-eye reflexes in humans with absent vestibular function are not so clear as in animals.^{28,29,30,31,32,33,34} The COR is considered to play a rudimentary role during high frequencies, low velocities, passive head movements and in subjects with normal vestibular function.^{35,36,37,38} During high-frequency passive head rotation, we consider the VOR found in our study not or minimally influenced by the COR.

Eye movement detection

Horizontal eye movements were recorded separately for each eye using EOG, with bilateral electrodes positioned on the outer canthi and lateral to the nose close to the eyes. Vertical eye position was recorded with electrodes above and below the right eye which detected eye blinking. A reference electrode was placed on the forehead above the bridge of the nose. Before each test, the horizontal EOG-lead was calibrated by predictable saccades of 20° visual angle (distance 1 meter, target 0.5°).

Data analysis

Data acquisition, storage and analysis of the data were performed by an eight channel Nystagliner system (software version 3.0, Toennies; Wuerzburg). In experiment 1 nystagmus activity was detected automatically. The average duration of all nystagmus activity to the left and right was calculated together with the nystagmus preponderance. In all experiments, fast phases and blinks were removed by automatic differentiation of the position signals followed by percentile and median filtering. Velocity gain, velocity preponderance, phase and coherence were calculated by fast Fourier transform.

mation.

In experiment 2, Fourier analysis resulted in a large number of frequency peaks at which velocity gain, phase and coherence were calculated. The spectral content, and therefore the location of the frequency peaks, varies between experiments which hampers determination of mean values and comparison of measurements. In order to permit comparison between measurements and between patients, the gain, phase and coherence at 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5 and 6 Hz were calculated by linear interpolation. In previous studies, the gain of the high-frequency VOR has shown an optimal reproducibility at 4 Hz; at this frequency visual cues have no influence (in contrast to lower frequencies) and the effects are linear (in contrast to higher frequencies).^{23,24} The response at 4 Hz was therefore used to assess the outcome. Coherence function was calculated in all tests to assess the validity of the data and to give an indication of the linear dependence between input and output. Results of a frequency analysis yielding coherence values of less than 0.93 were excluded.²⁵ Due to the length of the sessions, the attention and alertness of the patient was sometimes insufficient to obtain reliable measurements. This effect was reflected by low coherence or dysconjugation. Dysconjugation of more than 15% (both position and velocity) also resulted in exclusion of the data. Data excluded by one of the three criteria mentioned above, were treated as missing values in the statistical analysis.

Statistical analysis

Statistical analysis was performed using SPSS/PC version 4.0 (Microsoft). The normal distribution of group and standard deviations of individual values (ANOVA) was verified by normal probability plots. If necessary a Box-Cox transformation was applied to fulfill the normality criteria. A t-test (2-sample, cross-over design) was employed to compare betahistine and placebo. The relationship between dosage and effect was investigated by a two-way ANOVA.

RESULTS

Experiment 1: Low-frequency whole body rotation in the dark

Fig 1 shows the relative change in mean gain for each dose of betahistine compared with placebo over time; each dose-time relationship is corrected by subtracting the corresponding response at time 0 and the corresponding response at dose 0. The relationship between effect, dose and time was not markedly effected after correction for unequal distribution of data due to missing values. As shown here, this correction will reduce the variation where there is a systematic difference between patients. The maximum decrease in gain (20%) was seen 4 hours ($p=0.04$) and 6 hours ($p=0.01$) after administration of the 16 mg dose of betahistine. Higher doses appeared to abolish

this effect. However, this effect of the higher doses is not clearly seen in the individual data due to the poor reproducibility of the torsion swing test. Betahistine had no significant effect on the individual or mean phase, coherence, eye velocity preponderance, nystagmus duration and velocity, or nystagmus preponderance.

Figure 1. Effect of betahistine on change in velocity gain of VOR during low-frequency sinusoidal rotational stimulation as a function of time and dosage (mean values $\pm$ 2 SD, $n = 8-12$)

Experiment 2: High-frequency passive head rotation

Fig 2 shows the mean gain change at 4 Hz obtained from the amplitude spectra by linear interpolation. Data correction was performed as in experiment 1. A slight increase in gain was followed by a marked decrease of up to 50% at 4 and 6 hours after drug intake; the maximal dose was 32 mg. The time-dose dependency was not markedly affected after correction for missing values. Betahistine had no significant effect on individual or mean phase or coherence.

Figure 2. Effect of betahistine on change in velocity gain of VOR during high-frequency passive sinusoidal head rotation (4 Hz) as a function of time and dosage (mean values ± 2 SD, $n = 8-12$)

DISCUSSION

Betahistine had no effect on the duration of nystagmus induced by low-frequency sinusoidal whole body rotation in the dark in this group of patients. In contrast Oosterveld reported a large decrease in nystagmus duration at similar dosages of betahistine in a group of healthy volunteers.⁷ It was suggested that the effect of betahistine in volunteers was normalised in such a way that, in the current study, a maximum 5% decrease in nystagmus duration would be expected (personal communication). However, the sensitivity of our test is insufficient to detect such a small effect. The superior resolution reported by Oosterveld may be due to the fact that volunteers are more easily selected, trained and instructed than patients which, in turn, improves reproducibility and reduces variability.

A maximum of 20% decrease in the mean low-frequency VOR gain was found between 4 and 6 hours after administration of 16 mg betahistine. Surprisingly, this effect was less marked at higher dosages. The effect of betahistine on high-frequency VOR gain was also unexpected, with a maximum decrease of up to 50% observed between 4 and 6 hours after administration of 32 mg betahistine. Lower or higher doses showed a less pronounced effect. A small, but not statistically significant, increase in VOR gain was observed in the first 2 hours after administration. In contrast, Oosterveld reported a steady increase of the effect of betahistine on nystagmus duration, up to a dose of 64 mg, in healthy volunteers.⁷

The complex dose effect curves observed between low- and high-frequency rotational

testing cannot be explained that easy and will require further research as current neuroscience knowledge does not allow a simple explanation. Some neuropeptides seem to have a similar complex impact on neuronal activity as indicated in a review on the effect of drugs on vestibular compensation by Smith & Darlington.³⁹

Also, as patients have functional disturbances under investigation, any direct comparison with healthy volunteers must remain speculative.

The initial, neuronal phase of vestibular compensation seems to be affected by proprioceptive and vestibular cues, but hardly visual cues.³⁵ The recent findings that betahistine accelerates vestibular compensation might therefore point to an interaction with vestibular and proprioceptive input that are that important for the compensation process and that betahistine does not act on the visual and/or oculomotor pathways which are closely associated with the VOR.⁶

In the two tests performed here, the primary vestibular pathways (labyrinths, vestibular nuclei) are stimulated. In another study it was found, that the visuo-vestibular interaction test, including a visual input, was not affected by betahistine.⁴⁰ Thus, the VOR is only affected in case of pure vestibular stimulation at low frequencies or a combined cervical and vestibular stimulation at high frequencies. So an additional visual input even seems to impair the effect of betahistine. No simple explanation for the observed complex but reproducible and evident effect of betahistine upon the velocity gain can be put forward. This aspect urge us to expand our research in this field.

CONCLUSIONS

Betahistine reduced the VOR gain at low and high frequencies of rotation; the effect being more pronounced at high frequencies and at moderate dosages (16-32 mg). The passive high-frequency head rotation test appeared to be the most sensitive tool to quantify the effect of betahistine upon the vestibular system in this study. To explain the complex dose-dependency of the reductions of the VOR gain, it is suggested that betahistine acts upon neurotransmission at different sites simultaneously. The primary site of action might be in the vestibular nuclei where the labyrinthine and proprioceptive input converge.

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Chapter

7

Summary and general discussion

SUMMARY AND GENERAL DISCUSSION

The aim of this study was quantification of the Vestibulo-Ocular Reflex (VOR) during high-frequency horizontal head rotation by use of Electro-Oculography (EOG). Our experiments were started in normal subjects using active head rotation measuring head velocity by an angular rate sensor mounted on a headband as has previously been described by O'Leary et al.^{1,2} Using a headband fixed rate sensor we found a decreasing gain and an increasing phaselag with increased rotation frequency in contrast to O'Leary et al. and Tomlinson et al.^{1,2,3} This difference possibly can be attributed to a difference in analysing technique or registration technique of head velocity. The experiment using a biteboard fixed rate sensor indeed showed that gain and phase are close to 1.0 and 0° respectively over the whole frequency range between 2 and 6 Hz. The difference is probably explained by slippage of the headband relative to the head at the higher frequencies. Conclusion: head velocity is detected more accurately with the biteboard fixed sensor and experiments were continued by using this application.

It appeared that 60% of the subjects in the headband group and 38 % of the subjects in the biteboard group, did not show active head rotation frequencies exceeding 4.5 Hz despite intensive instructions. The difference might be due to the fact that the headband is less comfortable and slips along the head compared to the steady fixed biteboard and as mentioned above, does not sense real head velocity. This explanation was confirmed by the subjective sensations of the subjects. However, in the study of O'Leary et al. and Tomlinson et al. *all* subjects reached a frequency of 6 Hz.^{1,2,3} The study of O'Leary et al. of age-related responses of the VOR shows that head movements in some subjects of the elderly population were generally slower (less than 4 Hz).⁴ We could not confirm that the majority of normal subjects were able to reach active head rotation frequencies up to 6 Hz. Apart from differences with respect to training and subjects it might be that the frequency analyses differ to some extent. Contribution of higher harmonics and non-linearities introduce a major problem analysing the responses. If a person is asked to rotate the head at 6 Hz, but only reaches 3 Hz, spectral analysis will show a substantial head and eye velocity at 3, 6, 12, 24 Hz etc. Also, head velocity especially at higher frequencies is not sinusoidal and contains lower and higher non-harmonic components. In this example using our analysis, the response is only attributed to the maximum amplitude in the head velocity spectrum (3 Hz) and therefore shows no response at 6 Hz. According to our interpretation of the data-analysis performed by O'Leary et al., the second harmonics of the 3 Hz component might have attributed to the 6 Hz response etc. and enhance the high-frequency VOR gain artificially.^{1,2,4}

The aspect of reaching a limited frequency range in case of active head rotation has been overcome by Tabak et al. by using a computer driven headshaker which can rotate the head passively up to 20 Hz.^{5,6} Eye and head movements in their study were recorded using the scleral coil technique (SCT) and VOR responses to sinusoidal head movements were analyzed. From 2 Hz on they found an initial gain of 1, which steadily decreased with a minimum of approximately 0.8 at 8 Hz, and subsequently increased to 1.1-1.3 at 20 Hz. Phaselag increased from about zero to about 45° at 20 Hz. According to their idea we developed a passive head rotation test and in an effort to determine whether the VOR differed during active versus passive head rotation a direct comparison was made in a group of normal subjects (Chapter 3). Analysis of the VOR between 2-6 Hz using EOG resulted in approximately similar findings as compared with the scleral coil technique mentioned above. This might enable and facilitate a broad clinical application of high-frequency testing, because EOG is less invasive and easier to use in the clinic compared to the SCT. Above 5-6 Hz however the amplitude of the induced eye velocities is too small to be detected accurately with EOG.

The advantage of the passive test versus the active head rotation test was that during passive testing head movement was approximately sinusoidal, whereas during active head rotation head velocity showed many non-sinusoidal components. As a consequence the analysis was more precise and easier using passive head rotation.

It appeared in this study that during passive rotation, by means of a computer-driven headshaker, if responding properly to the stimulus, all subjects were able to reach rotation frequencies of 6 Hz. However, some (about 5%) subjects were unable to relax their neck muscles, which lead to an inefficient transfer of the stimulus upon the head. These subjects were excluded from further analysis. Upon active and passive isolated head rotation the VOR was found to be fairly optimal between 2-4 Hz with an almost constant gain of one and approximately no phaseshift. Above 4 Hz active head rotation resulted in a more optimal reflex as compared to passive rotation: during passive head rotation gain decreased to 0.82 at 6 Hz in agreement with Tabak et al.^{5,6} Collewijn et al. studied the VOR in active versus passive head rotation in low frequencies up to 1.33 Hz, using the SCT for detection of eye position.⁷ They found gain values being 3% lower during passive compared to active rotation in the light and 13% in the dark. Goebel et al. also studied the VOR during passive and active head rotation in low frequencies up to 1 Hz, using EOG for eye movement detection.⁸ At 1 Hz no difference in gain (approximately 0.90) during active and passive head rotation was found.

Anticipation might be a mechanism for a better VOR during active compared to passive head rotation. The eye movement strategy may contain a central motor programme, that optimises the VOR through the predictability of the target or movements and prior knowledge or experience with the task.^{9,10,11,12,13,14,15} The finding that there is a difference between active and passive head rotation above 4 Hz might point

to a substantial contribution of such a central motor programme to the VOR above 4 Hz.

Comparison of our data of passive high-frequency head rotation with high-frequency whole body rotation introduces some interpretation difficulties. Theoretically there is a difference between head and whole body rotation. In case of whole body rotation no cervical input to the vestibular system is achieved. The Cervico-Ocular Reflex (COR) is supposed to cause eye deviations in the opposite direction of body rotation in the absence of visual or vestibular stimulation.^{16,17} The COR, although virtually non-existent in normal animals, has been shown in labyrinthine-defective animals to become increasingly instrumental in restoring the slow compensatory eye movements which accompany head movements.^{18,19,20} For example, it was shown that in normal monkeys the COR contributes little (2-3%) to ocular stabilisation during rapid head movements. However, in the labyrinthectomised monkeys, the contribution of the passively induced COR to gaze stability increases to about 30%, while during active movements it apparently reaches values near 80%.¹⁹ In literature a large variability in human COR gains is reported, not only among normal subjects but also in patients with bilateral vestibular loss; the results are controversial.^{21,22,23} Several studies report a COR enhancement in patients with bilateral vestibular impairment.^{22,24,25,26} However it was also found, that the COR was best elicited during low-frequency stimulation^{16,24}, low stimulus velocities²⁷, active head movements²⁶ and with eyes closed^{6,22}. Thoden et al. found that the COR could be enhanced by the instruction to imagine head movement.²⁸ Besides, the COR, involving a multisynaptic pathway, has a latency of about 100 msec which makes it unlikely that the COR is functional at high stimulus frequencies.²⁹ We assume that the COR does not substantially contribute to the VOR found at high-frequency passive head rotation in normal subjects. It is possible, that in patients with bilateral vestibular impairment, the COR contributes somewhat to the ocular responses we detected, especially at the lower frequencies. Huygen et al. investigating 30 patients, found that the COR-gain was frequency dependent, decreasing from 0,7 at 0,1 Hz to 0,4 at 0,4 Hz.²⁴ Therefore it is unlikely that the COR contributes to a great extent to the ocular responses found in patients with bilateral vestibular impairment at the higher frequencies.

At high-frequency whole body rotation also other diffuse tactile, proprioceptive information reaches the brainstem which contributes to the perception of movement of the body or body components and may affect the VOR gain and phase. All these aspects point to a possible difference in data to be found when comparing whole body versus isolated head rotation. Some studies report an increase in gain up to 4 in higher frequencies. Keller and Benson studying monkeys and humans respectively during passive whole body rotation, found horizontal gain rising to 1.4 and 2 at 4 and 5 Hz respectively.^{30,31} In these studies however, eye velocity was compared to chair velocity

instead of head velocity and during whole body rotation at high frequencies head trunk and chair movements may differ considerably due to poor fixation of the various body components. This might be the reason, that gain was somewhat overestimated sometimes, which was confirmed in a study by Larsby et al.³² Hoshowski et al. however, measured gain during passive high-frequency whole body rotation with an angular rate sensor attached to a headband, thus comparing eye velocity to head instead of chair velocity.³³ He found an increase in gain, 1.0 at 2 Hz increasing up to 1.7 at 4 Hz. However, in this study the inaccuracies of the headband fixed sensor described previously might exist. Analysis of the data in literature suggests that the peak velocity of the stimulus (body or head velocity) does not affect the VOR gain to a large extent in the velocity range applied. So a difference in peak velocity could not explain the differences in gain of the VOR measured upon head or whole body rotation. Tabak et al. recently confirmed that even in isolated head rotation the VOR gain indeed slightly increases up to 1.3 at 20 Hz, although the gain started to increase only beyond 8 Hz.^{5,6} This effect is not large, but indicates that the difference between VOR gain between isolated head and whole body rotation needs further research.

Dayal & Tomlinson using pseudorandom whole body rotation of 2-5 Hz comparing normal subjects and patients with *Meniere's disease*, found that patients showed a gain exceeding normal values in the higher frequency range.³⁴ This increased gain was attributed to the acceleration sensitivity of the lateral semicircular canal afferents at high frequencies in patients. Phase values were not discussed. As discussed above these results should be interpreted with caution because inaccuracies in body and head fixation as well as head velocity detection often occurs in case of high-frequency whole body rotation.³⁵

An increasing phaselag of the VOR at higher frequencies was suggested to be a useful diagnostic indicator for Meniere's disease by Matthew et al. using the *active* Vestibular Autorotation Test (VAT).³⁶ Although no difference was found between normal subjects and Meniere's disease patients in the acute stage of the disease; in the chronic stage of the disease decreased gain and increased phaselags at higher frequencies were found. At 5 and 6 Hz 85% of the patients were found to have abnormal gain or phase values regardless the clinical stage. However, it must be stressed that Matthew et al. defined the normal range by the average ± 1 SD, which is a rather soft criterium.²⁶ If the more accepted criterium of ± 2 SD is applied less than 50% of the patients show abnormal values. The results of Matthew et al. show a tendency that the high-frequency VOR deteriorates in the chronic stage of the disease.²⁶ Quantification of low- (calorics) and high- (head rotation) frequency testing in a longitudinal study of Meniere's disease patients might inform us about the relation between test outcome and stage or severity of the disease.

O'Leary & Davis reported an increased velocity gain at high frequencies during the

vertical VAT (2-6 Hz) in 10 patients in the acute stage of Meniere's disease.² We were unable to reproduce their results, because in a pilot study performed in normal subjects it appeared impossible to detect eye movements accurately due to the poor linearity and reliability of the vertical leads applying EOG. Besides, it appeared to be even more difficult to reach high rotation frequencies during vertical rotation compared to horizontal rotation, and more eye blinking artefacts occurred. In summary: there is no conclusive evidence that the VOR at high-frequency *active* horizontal *head* rotation is affected in Meniere's disease patients.

One might hypothesise that in Meniere's disease anticipation and a central motor programme might compensate for vestibular loss at higher frequencies which might result in a good gain and phase during active head rotation and that the function loss can only be detected by use of non-voluntary stimuli. The observation that unpredictable high-velocity impulses are also useful in detection of 'low-frequency compensated' vestibular lesions supports this interpretation.^{5,6,37} Another hypothesis could be, that the COR contributes to the responses found, although in the higher frequencies applied this is unlikely.

To investigate whether the passive high-frequency head rotation test was able to distinguish between Meniere's disease patients and normal subjects, we studied 20 *patients with Meniere's disease* classified according to the AAO-HNS criteria (Chapter 4).³⁸ The gain of the VOR between 2-6 Hz and the phaselag between 2-3 Hz, showed to be almost similar in Meniere's disease patients compared to normal subjects. Above 3 Hz the phaselag in patients using passive head rotation was significant larger than in normal subjects. At 3 and 4 Hz the difference between normal subjects and patients is maximum, as above 4 Hz the accuracy of the measurements decreased too much to allow a reliable discrimination (see above). However, four patients, clinically defined as having Meniere's disease according to the AAO-HNS criteria, with normal calorics and a normal low-frequency VOR, had abnormal phase values during passive head rotation, which is suggestive for the relevance of evaluating the high-frequency VOR.

Vestibular tests using high-frequency head rotation in patients with *bilateral vestibular impairment* has not been performed to a great extent yet. Goebel & Rowdon studied 34 subjects with bilateral reduced caloric responses using active head rotation and whole body rotation, both at 0.5 Hz.³⁹ Roughly one third showed a decreased VOR gain compared to normal subjects in both circumstances. Hyden et al. studied the VOR during high-frequency whole body rotation.⁴⁰ At high frequencies (>3 Hz) all patients showed reduced VOR gains compared to normal subjects. At low-frequencies gain values were close to normal when using a predictable stimulus (sinusoidal). With a non-predictable (pseudorandom) stimulation gain values were significantly reduced even at lower frequencies. Patients with the most severe loss showed a phaselag at higher frequencies. It must be mentioned that gains were found to increase at higher

frequencies, which might be due to errors made in detecting head velocity as discussed above.

Tabak et al. studied 3 patients with bilateral vestibular impairment using passive high frequency head rotation.^{5,6} Eye position was detected by the SCT. Values of the VOR gain of these patients were clearly lower and phaselags larger, compared to normal subjects in the 2-8 frequency range. The patient who had only mild vestibular symptoms in daily life, showed better VOR gain and phase values. This might indicate that high-frequency VOR characteristics correlate with compensation and clinical recovery after bilateral vestibular impairment.

We studied patients with *bilateral vestibular caloric hyporeflexia* using passive high frequency head rotation (Chapter 5). It was observed that absence of the VOR during low-frequency whole body rotation did not imply absence of the VOR at high frequency passive head rotation. Patients with an absent VOR during low-frequency rotation had a tendency to show lower gains at higher frequencies as compared to patients with a normal low-frequency VOR.

After bilateral vestibular function loss, most patients return to near normal lifestyle but when high-skilled locomotor performances are demanded, man can not completely compensate for total vestibular loss. Most labyrinthine defective individuals experience imbalance and oscillopsia, which is a disturbing illusion of movement of the environment while walking or in other ways while moving the head rapidly.^{41,42} This transient blurring of vision during rapid head movements is a very common, but not compulsory finding, as was also reported by patients in this study.⁴³ One would expect that patients who experience oscillopsia would have more difficulty performing in high-frequency rotation tests. This could not be confirmed in this study, maybe because some patients find it very difficult to describe their specific sensations. A few patients reported persistent distressing postural unsteadiness or oscillopsia. Here vestibular compensation may have failed to occur, may be incomplete or may have been (partly) lost. Possibly some event during the early phase of the disease ("critical period") has effected the normal course of the vestibular compensation. It would be of value to find objective measures to show the difference between patients who do and those who do not recover well. The only finding in our study to this respect was that less disabled patients tended to have a relatively good high-frequency VOR. Except for one patient, we observed that patients with the best VOR gain at higher frequencies tend to perform better in daily life and considered themselves less disabled. The possible role of the COR in the compensation process in patients with bilateral vestibular impairment, was discussed earlier in this chapter.

The passive high-frequency head rotation test was shown abnormal in Meniere's disease patients and in patients with bilateral caloric hyporeflexia. This suggested a relationship between vestibular function and the high-frequency VOR. As betahistine

is known to affect either vestibular function or reduce vestibular complaints, we studied the effect of betahistine upon the VOR in patients responding positively to betahistine. We observed that betahistine had no effect on the duration of nystagmus induced by low-frequency whole body rotation in the dark in Meniere's disease patients. Oosterveld reported a 50-60% decrease in duration of nystagmus activity at similar dosages of betahistine in a group of healthy volunteers.³⁹ Oosterveld stated that the effect of betahistine in normal subjects was normalized in such a way that, in our patient study, a maximum 5% decrease in nystagmus duration could be expected (personal communication). However, the sensitivity of our test is insufficient to detect such a small effect. The superior resolution reported by Oosterveld might be due to the fact that volunteers can be trained and instructed better than patients which improves reproducibility and reduces variability.

We found a maximum 20% decrease of the mean low-frequency VOR gain between 4 and 6 hours after administration of 16 mg betahistine. The effect of betahistine on high-frequency VOR gain was also unexpected, with a maximum decrease of up to 50% observed between 4 and 6 hours after administration of 32 mg betahistine. Lower or higher doses showed a less pronounced effect. A small, but not statistically significant, increase in VOR gain was observed in the first 2 hours after administration. Oosterveld reported a steady increase of the effect of betahistine upon nystagmus duration, up to a dose of 64 mg in healthy volunteers.⁴⁴ This does not agree with results obtained in our study with respect to the VOR gain.

Several factors may account for the complex effect of betahistine on the VOR gain. Firstly, as patients have functional disturbances of the system under investigation, any direct comparison with healthy volunteers must remain speculative. Secondly, a U-shape dosage effect relationship has also been found for the effect of neuron peptides upon the firing rate of neurons in the vestibular nucleus.⁴⁵

The complex relationship between gain change and dosage in this study may be attributed to the complex histamine-receptor mechanisms involved. Histamine inhibits its own release at the H_3 autoreceptor, a process which can be antagonized by low concentrations of betahistine thereby facilitating histaminergic neurotransmission in the brain. However, at high concentrations of betahistine, the impact on the H_3 receptor system might be reversed or the H_1 -agonistic activity may be invoked, thus cancelling the effect.

This study supported the hypothesis that betahistine acts upon the vestibular system in the subjective responder population. The high-frequency passive head rotation appeared to be a more accurate test to detect the effect of betahistine compared to low-frequency whole body rotation test.

Future perspectives

Testing the VOR at high frequencies is attractive because it reveals the physiological range of head movements, but also because contamination of the VOR by the visual ocular control system is generally considered small or absent in the high frequency range.

A fairly recent development in testing the VOR, is the combination of both active and passive high-frequency head rotation tests. The advantage of the active head rotation test is that no expensive rotatory device is necessary and that it can be applied at the bedside. The disadvantage in our hands was however, that most normal subjects were not able to reach rotation frequencies of over 4 Hz. Besides, active head rotation resulted in many non-harmonic sinusoidal components, which complicated analysis of the data. Our results clearly indicated that active or passive head rotation tests are not reliable if a simple head mounted angular rate sensor is used for detection of head velocity.

In this research project passive head rotation resulted in 6 Hz head rotation in all subjects and in a more sinusoidal stimulus, which simplified the analysis. In patients with Meniere's disease and in patients with bilateral vestibular impairment the high-frequency head rotation test has proven to be a supplement to the standard vestibular tests routinely used in many clinics, such as caloric stimulation and the torsion swing test. However, in patient populations a large variability in results exist. For the time being we consider the passive high-frequency head rotation test designated for specialised vestibular centers. Small signals during high frequencies result in difficult signal analysis. We are still working to improve this aspect, so that the test will be broadly applicable.

The caloric stimulation test is the test mainly applied to distinguish left from right sided vestibular pathology. However, the stimulus is non-physiological and the test-retest variability is large. The high-frequency head rotation test as described in this thesis is not able to distinguish left from right sided vestibular pathology. Recent development shows promising results of tests using unpredictable high-velocity step displacements of the head.^{5,6,46,47,48,49} The frequency spectrum of such head movements contains high frequencies. The VOR responses found using these tests were evidently *asymmetrical* in patients with unilateral vestibular loss, even 1 year after the vestibular lesion was induced. Using high-velocity step displacements of the head a lower gain and a prolonged delay of eye movements were found when moving the head towards the side of the lesion. The VOR delay is considered to be a potentially significant parameter of vestibular functionality. This means that the side of vestibular impair-

ment can be assessed even after compensation is completed, if physiological stimuli are applied (high-velocity step displacement of the head). So far, these tests have been using the magnetic search coil technique for detection of head and eye movements. In a pilot study we have tried to reproduce the findings using EOG, which is more patient friendly and easier applicable. However, the eye movements using unpredictable high-velocity impulses could not be detected properly using EOG. This clearly limits the clinical applicability of the impulse test, as the magnetic search coil technique is semi-invasive and blurs vision after 20 minutes and is therefore clinically not widely accepted. Further development of alternative eye position detecting techniques such as video-oculography might be useful in this respect.

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Chapter
8

Samenvatting

Inleiding

Een primaire functie van het evenwichtsorgaan is de hersenen te informeren over bewegingen van hoofd en lichaam en oriëntatie ten opzichte van de zwaartekracht. Hierdoor ontstaat een goede ruimtelijke oriëntatie en lichaamsstabiliteit. Bovendien is het evenwichtsorgaan het primaire systeem, dat zorgt voor de vestibulo-oculaire reflex (VOR). De VOR wordt in het algemeen veronderstelt het scherp zien te ondersteunen, door het genereren van oogbewegingen die gelijk zijn in snelheid en tegengesteld aan de richting van hoofdbewegingen. Hierdoor staan de ogen vrijwel stil in de ruimte terwijl het hoofd beweegt. Tijdens langzame hoofdbewegingen speelt het visuele systeem een grote rol bij de oogbewegingen, maar tijdens *snelle* hoofdbewegingen is het evenwichtsorgaan het enige systeem dat zorgt voor de blikstabilisatie. Dit heeft tot gevolg, dat men bijvoorbeeld tijdens lopen of autorijden op een hobbelige weg toch verkeersborden goed kan blijven lezen. De VOR is het belangrijkste thema van onderzoek in dit proefschrift.

De meest gebruikte "fysiologische" test waarbij de VOR opgewekt en gekwantificeert wordt om een indruk te krijgen over de functie van het evenwichtsorgaan, is de draaistoeltest, waarbij het hele lichaam van de proefpersoon wordt rondgedraaid. Gezien de technische beperkingen van de meeste draaistoelen gebeurt dit vrijwel altijd bij lage frequenties (< 1 Hz). Als het al mogelijk was om de stoel sneller te laten draaien, zou het erg moeilijk zijn om hoofd en lichaam goed aan de stoel te fixeren. Het draaistoelonderzoek gebeurt in het donker, om zo de invloed van het visuele systeem te beperken. Juist hierdoor zijn de resultaten van het draaistoelonderzoek erg variabel en afhankelijk van de instructies die worden gegeven en de alertheid van de proefpersoon.

Willen we op andere wijze de "zuivere" VOR meten, zonder dat de blikstabilisatie door het visuele systeem beïnvloed kan worden, dan zullen we de reflex moeten meten tijdens hoge frequenties waar het visuele systeem te traag is om de oogbewegingen te kunnen beïnvloeden. Hiertoe zijn vrij recent zowel actieve als passieve hoog-frequente hoofdrotatietesten ontwikkeld. Met als bijkomend voordeel dat geen dure draaistoel nodig zou zijn.

De parameters om de VOR te kwantificeren zijn de gain, fase en coherentie. De *gain* is gedefinieerd als het quotient van oogsnelheid (V_{oog}) en hoofdsnelheid (V_{hoofd}). De optimale gain ($V_{\text{oog}} / V_{\text{hoofd}}$) bedraagt 1, zodat oog- en hoofdsnelheid gelijk zijn en het beeld van de omgeving op het netvlies stilstaat. De *fase* is gedefinieerd als het tijdsverloop tussen oogsnelheid en hoofdsnelheid gerelateerd aan de frequentie (het faseverschil wordt aangegeven in graden). Een optimale fase bedraagt nul graden,

zodat er geen vertraging in de beeldstabilisatie is. De *coherentie* is gedefinieerd als de vormgelijkheid van tussen oog- en hoofdsnelheid en informeert ons derhalve over de kwaliteit van de signaalregistratie en de validiteit van de data; een ideale coherentie is 1. Oogbewegingen in dit onderzoek zijn gemeten door middel van Electro-Oculografie (EOG). De hoofdsnelheid werd gemeten door een hoeksnelheidsmeter op een hoofdband en later op een biteboard.

Doel van het onderzoek

Het doel van dit onderzoek was het ontwikkelen, verbeteren en evalueren van testen om de VOR te kwantificeren tijdens hoog-frequente hoofdrotatie.

Hoofdstuk 1

In de algemene inleiding wordt ingegaan op de achtergronden van het onderzoek. Kort wordt de fysiologie van de VOR besproken en uitgebreid wordt ingegaan op de functie van de VOR. De onderzoeksopzet wordt kort weergegeven. In een pilot studie hebben we een vergelijking gemaakt tussen het meten van de oogbewegingen door middel van EOG en met magnetische inductie spoeltjes (scleral coil technique (SCT)). EOG is een methode met electrodes rond het oog. De SCT is een methode, waarbij spoeltjes op het hoornvlies van het oog worden geplaatst na verdoving. We hebben geconcludeerd, dat EOG een betrouwbare methode is om oogbewegingen te meten tot circa 4-5 Hz; de methode is patiënt-vriendelijk en makkelijk toepasbaar in de kliniek.

Hoofdstuk 2

De hoog-frequente *aktieve* hoofdrotatietest wordt ook wel de Vestibulaire Autorotatie Test (VAT) genoemd. Hierbij wordt de proefpersoon gevraagd het hoofd van links naar rechts te bewegen op geleide van een klik met toenemende herhalingsfrequentie (2-6 Hz). In dit hoofdstuk wordt de methode uitgebreid besproken.

10 Normale proefpersonen werden onderzocht, waarbij de hoofdsnelheid werd gemeten met de snelheidsmeter op een hoofdband. We hadden de indruk, dat door beweging van de hoofdband ten opzichte van het hoofd bij hoge rotatiefrequenties, onnauwkeurigheden ontstonden in de detectie van de hoofdsnelheid. Hierop werden 2 proefpersonen onderzocht met zowel een snelheidsmeter op een hoofdband als op een biteboard. Het bleek dat de gain werd onderschat en de fase werd overschat in de eerste groep bij gebruik van de hoofdband. Dit werd bevestigd in een groep van 21

proefpersonen met een biteboard. In deze groep bleef de gain 1 en de fase 0° tot 6 Hz. In tegenstelling tot de literatuur bleek een aanzienlijk percentage van de gezonde proefpersonen niet in staat actieve schudbewegingen te maken met een frequentie hoger dan 4 Hz.

Conclusie: door middel van de VAT kan de VOR op een reproduceerbare wijze worden gemeten in de hoge frequenties tot circa 4 Hz. mits de hoofdsnelheid wordt gedetecteerd met een biteboard.

Hoofdstuk 3

Aangezien tijdens actieve rotatie veel normale proefpersonen niet in staat bleken het hoofd actief in hoge frequenties te roteren, werd gestart met een *passieve* hoog-frequente hoofdrotatie test. Hierbij werd het hoofd passief geroteerd van 2-6 Hz. door middel van een computer gestuurde helm met motor naar het idee van prof. Collewijn uit Rotterdam. In dit hoofdstuk werd een vergelijking gemaakt tussen actieve hoofdrotatie en passieve hoofdrotatie bij 14 gezonde proefpersonen. Tijdens de passieve hoofdrotatie bereikte iedereen zonder problemen 6 Hz. De gain en fase bleven tijdens actieve rotatie optimaal, echter tijdens passieve rotatie daalde de gain tot 0.82 bij 6 Hz., de fase bleef wel optimaal 0° . In dit hoofdstuk wordt in de discussie uitgebreid ingegaan op de mogelijke oorzaak van het verschil tussen actieve en passieve hoofdrotatie en het verschil tussen hoofdrotatie en rotatie van het hele lichaam.

Hoofdstuk 4

M. Menière wordt in het algemeen beschouwd als een ziekte van het binnenoor, welke resulteert in de klassieke trias van symptomen: aanvallen van vertigo, eenzijdig perceptief gehoorsverlies en tinnitus. Er bestaat een grote variabiliteit in de uitkomsten van de twee meest uitgevoerde vestibulaire testen bij M. Menière. 30-50 Procent van de patiënten met M. Menière heeft normale responsies bij de calorisatie en het draaistoelonderzoek. De uitkomsten van deze laag-frequente vestibulaire testen worden niet meer meegenomen in de meeste recente internationale classificatienormen (AAO-HNS 1995). Dit wetende zijn we begonnen om de hoog-frequente passieve hoofdrotatietest toe te passen bij 20 patiënten met M. Menière. Boven de 3 Hz. werd bij de patiënten een significant grotere fasenaloop gevonden in vergelijking met normale proefpersonen. Interessant was, dat bij 4 patiënten met een normale calorisatie en draaistoelonderzoek, een afwijkende VOR werd gevonden tijdens hoge frequenties. Tussen 3-4 Hz. was het discriminatieve vermogen van de hoogfrequente test het grootst.

Hoofdstuk 5

Uit de kliniek is bekend, dat patiënten na uitval van een evenwichtsorgaan een opvallend vermogen hebben om dit verlies te compenseren, zodat de klachten vaak meevallen zelfs bij een dubbelzijdig verlies. Het vaststellen van de vestibulaire restfunctie bij patiënten met een dubbelzijdige uitval is een probleem. Calorisatie wordt beschouwd als equivalent aan stimulatie met een lage frequentie, zodat men kan veronderstellen, dat de resultaten van hoog-frequente testen niet in alle gevallen overeenstemmen met de calorisatie. Meer specifiek; een calorische onprikkelbaarheid betekent nog niet vestibulaire uitval. In dit hoofdstuk werden de resultaten beschreven van de passieve hoog-frequente hoofdrotatietest bij 8 patiënten met een bilaterale calorische hypo- of areflexie. We vonden bij alle patiënten een substantiële VOR boven 2 Hz., maar de gain boven 4 Hz. was bij alle patiënten lager in vergelijking met normale proefpersonen. Een verkennende discriminant analyse toonde, dat de combinatie van de gain bij 4.5 Hz. en de gain bij het draaistoelonderzoek een goede correlatie bleek te hebben met de klachten van de patiënt. Resultaten van de calorisatie hadden in dit onderzoek geen toevoegende waarde met betrekking tot de klachten van de patiënt.

Hoofdstuk 6

Betahistine wordt verondersteld de vestibulaire functie te beïnvloeden en zo klachten te doen verminderen. In dit hoofdstuk werd onderzocht of een hypothetische vestibulaire functieverandering door betahistine een verandering geeft in de responsies tijdens de hoog-frequente passieve hoofdrotatietest. Deze dubbel-blind placebo gecontroleerde studie vond plaats bij 12 patiënten met paroxysmale vertigo, die baat meenden te hebben van betahistine. Direct voor en 1,2,3,4,6 en 8 uur na intake van 16, 32 of 64 mg. betahistine, vond een draaistoelonderzoek plaats en tevens de hoog-frequente passieve hoofdrotatietest. Betahistine beïnvloedde de gain tijdens het laagfrequent draaistoelonderzoek, maar meer nog de gain tijdens de hoog-frequente hoofdrotatietest. Het effect van betahistine was maximaal bij een gemiddelde dosis van 16-32 mg. Om de complexe dosis afhankelijkheid van het effect te verklaren werd verondersteld dat betahistine de neurotransmissie op meerdere plaatsen in de hersenen, waaronder in de vestibulaire kernen, gelijktijdig beïnvloedt.

DANKWOORD

Allen die hebben bijgedragen aan het tot stand komen van dit proefschrift wil ik hartelijk bedanken.

De vele proefpersonen die hebben deelgenomen aan de experimenten wil ik via deze weg nogmaals dank zeggen; zonder hen zou het zeker nooit gelukt zijn.

Prof. Dr. J.J. Manni, beste Hans, de afgelopen jaren heb ik in velerlei opzichten van je kunnen leren. Grote bewondering heb ik voor de consciëntieuze aanpak van alles wat je doet. Bij het lezen van de gecorrigeerde versie van mijn thesis -bijvoorbeeld- voelde ik mezelf soms erg slordig. Hartelijk dank voor de gelegenheid, die je me hebt geboden aan dit proefschrift te werken, je bijdrage en de fijne samenwerking in de afgelopen jaren.

Dr. H. Kingma, beste Herman, zonder jou onuitputtelijke energie en enthousiasme was het nooit gelukt en dan heb ik niets teveel gezegd. Soms wat chaotisch, maar altijd geweldig motiverend en stimulerend. Ik ben blij dat ik deze beklimming heb beléefd, zeker met jou als gids in de buurt.

Dr. E.H.M.A. Marres ben ik zeer erkentelijk, dat hij me heeft gestimuleerd om met dit onderzoek te beginnen.

Marlies, met veel plezier denk ik terug aan onze samenwerking. Altijd stond je er, als ik je lastig viel met vervelende vragen en met de vraag of je me "even" wilde helpen (ik zal waarschijnlijk niet de laatste zijn). Hartelijk dank.

Ron en Iwan, jullie waren vaak mijn redders in nood, als er weer eens een experiment of computer vastliep. In jullie afwezigheid durfde ik amper met een proefpersoon aan de slag te gaan. Bedankt voor de plezierige samenwerking.

Suzan, dank voor je enthousiaste inzet tijdens je stage en bijdrage aan de introductie.

Collega's assistenten, Ingrid, Jan-Willem, Joost, Patrick, Jaap, Jan, Janny, Liesbeth, Lysandra en Michèl, het was fijn om zo nu en dan af te kunnen reageren in onze kamer. De computer is nu weer helemaal van jullie. Jaap, samen met jou heb ik de eerste moeilijke stappen op het "vestibulaire pad" gezet, wat leerzaam maar vooral erg gezellig was. Nu is het jou beurt om het af te ronden.

Lieve pap en mam, bedankt voor jullie nooit aflatende steun en interesse in alles wat we doen.

Lieve Marcel, het is ongelooflijk zoals jij vanaf het begin betrokken en geïnteresseerd bent geweest in dit onderzoek. Mede dankzij jou is dit proefschrift geworden wat het is. Steeds had je weer nieuwe ideeën om sneller en efficiënter te kunnen werken en om de lay-out nog mooier te maken. Je wist me ook vaak weg te slepen van de computer om van het leven te genieten, wat we ook zeker gedaan hebben. Dankjewel.

CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 25 januari 1964 te Lage Mierde. Het eindexamen VWO werd in 1982 behaald aan het Rythoviuscollege te Eersel. In hetzelfde jaar startte zij met de studie Geneeskunde aan de Katholieke Universiteit Nijmegen. Tijdens en vlak na het afronden van deze studie deed zij onderzoek bij de vakgroep Keel-, Neus- en Oorheelkunde (KNO) aldaar naar de resultaten van gehoor-beenketenreconstructies met homoloog materiaal. Het artsexamen werd behaald in maart 1990, waarna ze van augustus t/m december 1990 werkzaam was als AGNIO KNO Academisch Ziekenhuis Nijmegen. Hierna, van februari tot augustus 1991, was zij werkzaam als Senior House Officer, Ear Nose and Throat in het Queen Elisabeth Hospital in Birmingham, Verenigd Koninkrijk. Van 1991 tot 1996 werd de opleiding tot KNO-arts genoten in het Academisch Ziekenhuis Maastricht onder leiding van Prof. Dr. E.H.M.A. Marres en later Prof. Dr. J.J. Manni. De B-opleiding vond plaats in het De Wever Ziekenhuis in Heerlen onder leiding van Dr. T.D. Zylker. Tijdens de opleiding werd het onderzoek verricht, wat geleid heeft tot dit proefschrift. Momenteel is zij werkzaam in de KNO-maatschap Arnhem-Velp-Zevenaar.