High-frequency testing of the vestibular system

General discussion and valorisation

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

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

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

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

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

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

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

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

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

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

How to perform a VHIT

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

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

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

Future research

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

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

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

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