

Fundamental studies to assess and restore vestibular function in patients with severe bilateral vestibular loss

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Chapter 9 Final discussion and valorization

THE AIM AND FINDINGS OF THIS THESIS

Many people worldwide suffer from bilateral vestibulopathy (BVP) which prevalence is estimated at 0.03% in the whole population (Ward et al., 2013) (Agrawal et al., 2009). Patients with BVP usually report lower health-related quality of life (HRQoL) (Guinand et al., 2012; Sun et al., 2014). Unfortunately, BVP is still often misdiagnosed due to diagnostic challenges like the lack of standardization in vestibular testing (Van De Berg et al., 2015). Furthermore, treatment options are currently limited and with low yield (Van de Berg et al., 2011). Therefore, this thesis aimed to improve the diagnostics and optimize treatment of BVP by electrical stimulation based on investigation of underlying physical principles. Topics considered in this thesis included the following: patterns of the vestibular dysfunction in BVP patients, video head impulse testing using electro-oculography, assessment of self-motion perception, and electrical properties of the inner ear that are used in electrophysiological models for optimizing electrical stimulation by a vestibular implant (VI).

In this thesis, it was demonstrated that:

- Only three quarters of patients diagnosed with bilateral vestibulopathy are eligible for vestibular implantation because it requires a careful examination of all five vestibular end organs to ensure safe implantation of the vestibular implant.
- Electro-oculography detecting the electrical potential of an eye is an accurate alternative to video-oculography in head impulse testing.
- Thresholds of self-motion perception can quickly be determined in a clinical setting using a six degrees of freedom motion platform, but different testing paradigms need different normative values.
- The electrical double layer of inner ear tissues, together with medium polarization, plays a significant role in the electrical impedances, and should be considered in electrical conductivity models to optimize vestibular implant stimulation.

FINAL DISCUSSION AND VALORIZATION

Bilateral vestibulopathy (BVP) is a chronic disease characterized by a bilaterally reduced or absent vestibular function (Hain et al., 2013; Lucieer et al., 2016; Strupp et al., 2017). According to Barany Society criteria, BVP is diagnosed based on symptoms (e.g. unsteadiness and oscillopsia) combined with a bilaterally reduced vestibular function as measured by at least one of the following tests: caloric test, torsion swing test, and head impulse test (HIT) (Strupp et al., 2017). However, these tests only measure the vestibulo-ocular reflex of the horizontal semicircular canals, while BVP is not a homogeneous disorder: abnormalities can also be found in the vertical semicircular canals and otolith organs. Therefore, to better understand BVP, it is recommended to evaluate the function of all five end organs. This will also facilitate decision making regarding vestibular implantation. After all, since surgically

implanting the vestibular system can cause significant damage to the vestibular system, other sensors than the horizontal semicircular canals also need to show deficits. By this, the vestibular system is not additionally damaged by vestibular implantation (van de Berg et al., 2020). Moreover, regarding diagnosis of BVP, the caloric test and video head impulse test seem to have a higher sensitivity for detecting vestibular hypofunction: 80% of BVP patients were diagnosed based on only the caloric test, only video head impulse testing, or both tests (Chapter 2).

Vestibular test procedures based on the vestibulo-ocular reflex, mainly use recording of eye movements (oculography) (Blakley & Chan, 2015; Eggert, 2007; Siddiqui & Shaikh, 2013). The gold standard of eye movement recording, the scleral coil technique, is almost never used in clinic due to its inconvenience for the patient. Video-oculography is most widely used, but it has drawbacks related to pupil detection, calibration, goggle slippage, and fitting the predefined geometry of the goggles to a patient's face (Heuberger et al., 2018; MacDougall et al., 2009; Suh et al., 2017; Weber et al., 2009). Electro-oculography is nowadays less commonly used in clinic, but it is still a complementary technique which can reliably be used for eye movement recordings during the caloric test and during rotatory chair testing (Ganança et al., 2010; López et al., 2016; Merino et al., 2010; Pietkiewicz et al., 2012). The feasibility of using electro-oculography for video head impulse testing, was not yet investigated. This thesis demonstrated that electro-oculography is an accurate technique to record eye movements during horizontal video head impulse testing: results are not significantly different from video-oculography (Chapter 3).

Many vestibular testing procedures rely on vestibular reflexes (Lang & McConn Walsh, 2010; van de Berg et al., 2018), while the function of the vestibular system goes beyond facilitating reflexes. Testing reflexes only, implies that the vestibular system is not fully tested by current clinical tests (Merfeld et al., 2014). Therefore, an additional vestibular test was proposed: testing of self-motion perception thresholds (Dupuits et al., 2019). Self-motion perception is a much more complicated mechanism than vestibular reflexes, since it is the end-result of a multisensory integration of signals, including input from the audiovestibular, visual and somatosensory systems, which are modulated by cognition (Merfeld et al., 2005; Nouri & Karmali, 2018). In addition, the surrounding three-dimensional space allows 12 different motion types and directions: six translations along three orthogonal axes and six rotations around the same orthogonal axes. Each of these directions is sensed by different vestibular end organs, and, therefore, motion sensitivity will be different for each type of motion. In research setting, test duration is one of the most fundamental problems when measuring the 'true' self-motion perception thresholds. After all, a long test procedure leads to decreased attention, compromising test results. In this thesis, a relatively fast (<1 hour) procedure was described to determine self-motion perceptual thresholds in clinic. It was demonstrated that self-motion perceptual thresholds could reliably be obtained and that thresholds increase with age, probably indicating the decay in the vestibular function. Another study recently found that BVP patients demonstrate significantly

higher self-motion perceptual thresholds for certain movement types and directions (van Stiphout et al., 2021). This might imply that self-motion perceptual thresholds can become another functional outcome (in line with DVA (Starkov, Snelders, et al., 2020) and fHIT (Starkov, Guinand, et al., 2020; van Dooren et al., 2019)) related to vestibulopathy, complementing the vestibular test battery. (Chapter 4).

It should be noted that for self-motion perceptual thresholds, the chosen testing paradigm influences the thresholds. It was shown that reducing the number of choices leads to a decrease of the self-motion perceptual thresholds (Grabherr et al., 2008; Priesol et al., 2014). Most likely, this is mainly the result of a higher chance to guess the correct type and direction of movement. This means that if 12 possible options are presented, an 8% chance to guess the right threshold is present, and with only two options, this chance increases up to 50%. However, an additional psychometric influence cannot be ruled out. This latter was not investigated, since the subject of the study in this thesis was related to clinical outcomes (yes or no a decrease of thresholds), not to the full underlying mechanism of the change in threshold between two testing paradigms (12 options versus 2 options). The findings of this thesis imply that normative data should be collected for each testing paradigm. Therefore, when using self-motion perceptual thresholds in future diagnostic procedures and studies, findings should be related to the testing paradigm specific normative values (Chapter 5).

Since the vestibular implant (partially) restores vestibular function by electrically stimulating the vestibular system, it seems necessary to gain more insights in how the electrical current flows through the vestibular system. After all, having a deeper understanding of this current flow, might allow more safe and effective stimulation of the vestibular system. For this purpose, electrophysiological modelling of the inner ear is imperative (Handler et al., 2017; Hayden et al., 2012; Marianelli et al., 2015). Several factors are involved in optimizing the accuracy of such a model. First, the geometry, structure and size of the inner ear need to be determined with high resolution (micro)CT scanning techniques (Ertl & Boegle, 2019; Glueckert et al., 2018; van den Boogert et al., 2018) (Chapter 6). In case of creating a personalized model for already implanted patients, electrode position can be checked postoperatively, using e.g. three-dimensional X-ray tomography. Other factors that influence the current flow are the electrical properties of the inner ear that can be described in terms of the electrical impedance (Chapter 7). Although research in animals might not fully represent the human situation, it can still provide essential insights about current flow to validate existing models. In this thesis, the guinea pig inner ear's measured impedances identified the key physical phenomena that influence the current flow: electrode and medium polarization. Eventually, the impedance will determine whether stimulation is possible or not: a high impedance most probably indicates a suboptimal contact between one of the stimulating electrodes and the tissue it aims to stimulate, compromising effective electrical stimulation.

Finally, the precise pathway of current flow in the inner ear, and the amount of current delivered to the target nerve, can be obtained from these three-dimensional electrophysiological models. The existing models described in literature have different complexity, incorporating more or fewer tissues. These models strongly rely on the electroconductive parameters of every tissue, while it is known that these parameters are not precise. Combining the 3D geometric model of the inner ear and the experimental measurements described in Chapter 7, allows more precise estimates of the required parameters (electroconductivity and permittivity of the double layer, endo- and perilymph, and temporal bone) and evaluates the significance of the presence or absence of every tissue in the model: the presence of the temporal bone around the inner ear significantly changes the electrical impedance measured inside of the inner ear. The resulting experimentally validated electrophysiological models might aid in determining the best electrode position and stimulation paradigm, in order to improve safe and effective stimulation of the vestibular system using a vestibular implant (Chapter 8).

FUTURE RESEARCH

Bilateral vestibulopathy and its relation to underlying etiologies

Despite existing diagnostic criteria for diagnosing bilateral vestibulopathy, the use of different equipment and data processing algorithms might result in different outcomes and diagnoses (e.g., a patient might not be classified as BVP even though the disease is present). Therefore, vestibular testing should also include normative data related to the system used and standards regarding vestibular test procedures should be formulated world-wide. Collecting a more extensive and complete database of BVP patients, including the function of all five end organs, might improve understanding of BVP in general and in particular the idiopathic etiology.

Reliability of the electro-oculography method in head impulse testing

Development of a light-weight electro-oculography based device that includes gyroscopes, a multichannel amplifier and signal processing and analysis software, could result in a new type of head impulse testing device, complementary to the video-oculography devices. For that purpose, the following is required: 1) testing the applicability of electro-oculography in vertical head impulse testing; 2) testing the applicability of electro-oculography in patients with vestibular hypofunction. If successful, electro-oculography might especially be a useful alternative for patients in which video-oculography is challenging (e.g. difficulties with pupil detection). Furthermore, costs might not be as high as for the video-oculography devices, although that should still be determined.

Self-motion perception testing and the vestibular implant

At current, it was demonstrated that the vestibular implant is able to restore the vestibulo-ocular reflex, dynamic visual acuity, and spatial orientation.

Nevertheless, how much the vestibular implant contributes to motion perception, remains unknown. Testing of self-motion perceptual thresholds in bilateral vestibulopathy patients fitted with a vestibular implant, might therefore indicate whether the vestibular implant is also able to improve self-motion perception. In addition to this, testing self-motion perception during electrical vestibular stimulation might also bring new insights into the interaction between the peripheral vestibular end organs and the brain. After all, the advantage of the vestibular implant is the fact that it can (relatively) selectively stimulate different parts of the vestibular organ. Whether this eventually results in specific improvements of self-motion perception, still needs to be determined.

Optimization of electrical stimulation of the vestibular afferents

Investigating in vivo the electrical impedances in bilateral vestibulopathy patients fitted with a vestibular implant, can give additional insights in the tissue properties and how to improve the electrophysiological models' accuracy. By developing more precise models of the inner ear's electroconductivity (in terms of substructures and their electrical properties) could eventually lead to a more personalized and effective stimulation paradigm in vestibular implant patients. Furthermore, otolith structures should be included in the electrophysiological human models, to facilitate the electrode design, surgical approach and stimulation paradigm which are necessary for electrical stimulation of the otolith organs.

This thesis demonstrates the importance of developing and implementing new diagnostic tools and treatment options in routine clinical practice. Moreover, an efficient and cost-effective approach to restore vestibular function using a vestibular implant will reduce patients' suffering and socio-economic burdens on societies. This thesis and future projects will aim at developing, identifying, improving, and implementing efficient diagnostic tools and treatment options in practice, to improve quality of life in patients with vestibular hypofunction.

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