The Vestibular Implant

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Final discussion and valorisation
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The success of the development of a medical device heavily depends on the proper criteria for patient selection. However, criteria can only be formulated by having validated insights in the real problems that patients encounter. Currently, many unresolved challenges are met when interpreting the standard diagnostic tests. It is imperative that the recently developed diagnostic criteria for bilateral vestibulopathy (BV) (Strupp et al., 2016) are complemented by deeper insights in these challenges. This will not only lead to better patient selection for a VI, but also to better effect evaluation (Chapter two).

In 2009 the VI-project was extended from Geneva to Maastricht, creating the Geneva-Maastricht team. All available information from previous research was used to proceed with experiments in humans (Chapter three). One of the first choices was to add the intralabyrinthine approach to the surgical techniques. This was previously not performed due to several reasons. Next to the risk of hearing loss, a main concern comprised the chance of not being able to elicit a response, as a result of “dying back” of the nerves after a long-standing loss of vestibular function. Previous intralabyrinthine approaches were only performed in animals in which a vestibular loss was recently induced by canal plugging or ototoxic medication, not addressing the effect of “dying back” of the nerves. By intraoperative intralabyrinthine stimulation of the vestibular system in a patient with a long-standing vestibular loss, it was shown that intralabyrinthine stimulation was at least feasible in a subset of patients with BV. It paved the way for the use of the intralabyrinthine approach for vestibular implantation in humans (Chapter four).

After showing the first results of a real vestibular prosthesis in humans (Perez Fornos et al., 2014), not included in this thesis), a total overview was desired about all the results obtained so far in the first 11 patients implanted with the vestibular implant prototype. Publishing these results provided more clarity and illustrated the feasibility of a VI, whilst at the same time showing that many challenges needed to be met in order to get a clinically useful device (Chapter five).

One of these challenges is the stimulation paradigm. Animal research has shown that gain, alignment and asymmetry of the response can be improved by optimizing the stimulation paradigm (Davidovics et al., 2012). However, some characteristics of the natural response are frequency dependent. Therefore, the natural frequency-dependency of the VOR is an aspect that could be taken into account with respect to the stimulation paradigm. If the response elicited by the VI shows other frequency-dependent characteristics than the natural vestibular system, the stimulation paradigm might have to be adjusted to compensate for this difference. Therefore, the frequency-dependency of the VI was tested in 7 implanted patients and compared to a group of age-matched healthy volunteers. It was shown that the VI closely mimicked
the frequency-dependency of the natural vestibular system in the tested frequency range (0.5 to 2Hz) (Chapter six).

Another factor to take into account is the residual natural vestibular function. Many patients suffering from BV (who might benefit from a VI) still have some residual “natural” vestibular function. This residual “natural” function could potentially interact with the “artificial” function of the VI in dynamic situations. Chapter seven demonstrated the presence of an interaction between the “natural” vestibular input and the “artificial” VI-input in the acute phase of stimulation. Whether this interaction still exists after the acute phase, has yet to be investigated in chronic stimulation trials. Nevertheless, the presence of this interaction is an important finding, since it might be taken into account during the initial phase of “fitting” of the VI. It could also be of benefit when trying to counteract vestibular asymmetry as occurring during disabling attacks of vertigo. If a fluctuating residual natural vestibular function would elicit an attack of vertigo, the VI could interact with it and might be able to “overrule” the residual natural function. This would result in the VI having control of the vertigo-attack and the patient feeling less vertiginous. The VI could then serve as an alternative therapeutic strategy in e.g. Meniere’s disease. However, whether this interaction is beneficial or counterproductive in these situations, has not been determined yet. Next to this, many non-linearities were found in the eye movements resulting from VI stimulation. This initiated the development of a new method of eye movement signal analysis. It implies that previous findings of VI experiments should be interpreted with care.

Animal research and the first experiments in humans mainly focused on the VOR. However, creating an optimal VOR-response with the VI, does not necessarily indicate a functional benefit for the patients. Other outcome parameters should be taken into account. One of these alternative parameters is the dynamic visual acuity, since it can be decreased in BV patients. For the first time in the world, a real functional benefit of the VI was demonstrated in a placebo-mode controlled trial: The dynamic visual acuity significantly increased by the VI (Chapter eight).

All things considered, a VI seems to be feasible as a therapeutic device for (at least) BV patients. However, many aspects should still be investigated or developed, before the VI can be considered as a clinically useful medical device. These aspects will be discussed below.

**Surgical technique and electrode design**

Regarding VI surgery and electrodes, the ultimate goal is to get the VI-electrodes as safe and simple as possible at the desired location of stimulation, whilst preserving inner ear function. For future investigations, this implies a more thorough exploration of the intra- as well as the extralabyrinthine approach and tailor-made electrodes.
facilitating these approaches. Surgical techniques should become more standardized and accessible, while also taking into account “soft surgery” in order to preserve inner ear function. The electrodes should be designed in such a way that positioning is easy and without any significant damage to adjacent structures, while at the same time facilitating optimal stimulation with the possibility of e.g. reducing current spread. The Geneva-Maastricht team is currently working on optimization of surgical techniques with corresponding electrode designs.

Optimization of signal analysis
At this moment, most of the VI-research uses techniques for signal analysis with many “old-fashioned” pre-assumptions about the expected VOR-response. However, preliminary results showed a more complex VOR-response than expected previously. In order to measure the VOR-response as purely as possible, new techniques for signal analysis have been developed that do not force signals into expected patterns, but are more open to variability in time and the non-linearity of the response. The Geneva-Maastricht team is currently working on optimization of the signal analysis, in close cooperation with the faculty of physics of Tomsk State University, Russia.

Optimization of the stimulation paradigm and transfer function
After optimization of the signal analysis, the optimization of stimulation paradigm and transfer function can be realized. This is necessary to eventually provide the vestibular system with a VI-stimulation pattern that facilitates an output that mimics as closely as possible the output of the natural vestibular system for a given input. Challenges that will have to be met are e.g. current spread, different dynamic ranges for each electrode and the non-linearity of the VI-response. The stimulation paradigm and transfer function are currently investigated using a biophysical approach by the Geneva-Maastricht team in close cooperation with the faculty of physics of Tomsk State University, Russia.

Optimization of effect evaluation
The VI offers a whole new approach for stimulating the vestibular system. This implies that conventional methods of effect evaluation using e.g. the VOR, the vestibulo-colic reflex, posturography and dynamic visual acuity, might not be sufficient. However, in order to know what effects can be expected, it is important to first gain insights into the abnormalities that can be expected in BV. At this moment, sufficient knowledge about BV is lacking regarding e.g. perception, walking, cognition, patient expectations, health related costs and the relation between different testing parameters. After having this structurally analyzed, new methods of effect evaluation can be developed, that go “beyond” the traditional methods of effect evaluation. The Geneva-Maastricht
team is currently investigating patient expectations, health related costs and patient characteristics in patients with BV, aiming at the development of new methods of effect evaluation. This research is conducted in close cooperation with the Department of Clinical Epidemiology and Medical Technology Assessment of the University of Maastricht.

**Development of criteria for vestibular implantation**

Recently, diagnostic criteria have been developed for BV (Strupp et al., 2016). However, definite criteria for vestibular implantation have not yet been developed. The previously mentioned study of patient expectations and patient characteristics will also be used to support the development of these criteria. After having implanted BV patients in a trial with chronic stimulation, it could be considered to expand the implantation criteria to other diseases like unilateral vestibular hypofunction, attacks of vertigo (e.g. using the VI as a “vestibular pacemaker”, if possible) and presbyvestibulopathy.

**Development of rehabilitation strategies**

After implantation, patients should get used to the VI as fast and safe as possible while maximizing the benefit. Just like cochlear implant recipients need to learn how to “hear” with the implant, VI recipients need to learn how to use the new vestibular information for image stabilization, balance and spatial orientation. However, how they should learn this, is currently an open question since “maintaining” balance is a multimodal task. This implies that the VI “adds” information to an already active system, instead of providing the sole input. Rehabilitation should imply integration of all the sensory systems involved and the use of the strong adaptive capacities of the brain. The content of rehabilitation will probably take shape during the chronic stimulation trials.

**Optimizing biomechanical aspects**

The first VI’s were prototypes and consisted of research software, big batteries, big processors, etc. In order to become a medical device, the VI should be a small, lightweight and portable device with strong batteries and sensors firmly attached to the head. Ideal situation would be to have the most components of the VI in the external part, facilitating continuous updates without having to manipulate the implanted parts. This means that many biomechanical aspects should be optimized. The Geneve-Maastricht team is currently working on these aspects in close cooperation with Medel.
Development of a second prototype V(C)I

The above-mentioned topics are all necessary to eventually develop a second prototype VI suited for a more extended clinical trial with chronic stimulation. Since several research groups are currently addressing the topics, both the prototype and set-up of the new trial will probably consist of inventions from more than one research group. Medel and its research partners have already given the initial impetus to this trial.

This thesis illustrates that BV is a disease with an important impact on quality of life that imposes a socioeconomic burden on society. Since current treatments options are limited and with low yield, a more substantial treatment is needed. This thesis has shown the feasibility of a VI and it has paved the way for newly already initiated research projects. These projects will define more thoroughly all aspects necessary to have the VI as a clinically useful device. After that, hopefully in the near future, we will be able to provide a more substantial treatment for patients suffering from loss of vestibular function.
References

