Advancement in cVEMP’s

CHAPTER 6

Final discussion and valorisation

FINAL DISCUSSION AND VALORISATION

Since the renewed description of cVEMP's in 1994 the effect of muscle activation on test outcome has been described. The papers in this thesis are the first to systematically evaluate the effect of normalization (i.e. correcting for muscle activation) and to assess which method is most effective. Also, by reducing test time, demonstrating the ability to differentiate between pathologies and evaluating which outcome measure is most useful the clinical implementation of cVEMP has improved.

Current state of the art physiological tests available in diagnosing Meniere's disease show that there is no test that can prove Meniere's disease, especially in its early stages (chapter 2). Also, since the exact pathophysiology of Meniere's disease is still unclear, it is possible that patients with similar complaints have different underlying pathologies that can be distinguished more accurately as diagnostic abilities improve. For instance, we now know that clinical symptoms of vestibular migraine greatly overlap with Meniere's disease. Given the fact that vestibular migraine is much more prevalent compared to Meniere's disease, it is likely that patients with vestibular migraine have been (mis)diagnosed with Meniere's disease in the past. The distinction between the two entities is much better defined nowadays, although it can still be a challenge to distinguish the two in practice. Since diagnostic criteria have become better described, it is important to have well evaluated tests that aid in the diagnosis of different pathologies. This thesis describes a number of studies aimed to improve cVEMP testing and its clinical use, such as aiding in differentiating between vestibular migraine and Meniere's disease.

In cVEMP literature correcting for muscle activation has already been described (e.g. Welgampola 2001). By systematically evaluating the effect of normalization we showed that by correcting the EMG for muscle activation the variability of the cVEMP can be reduced significantly in normal subjects (chapter 3.1). Since the cVEMP response is largely linearly related to muscle EMG, correcting for differences in muscle strength makes sense. This means that when testing a person with a small SCM muscle contraction or a person with a strong SCM muscle

contraction, the influence of muscle strength will be reduced and thereby reflect saccular function more adequately. By reducing the variability, and thereby obtaining a more uniform

cVEMP outcome, it could also improve the ability to distinguish between a healthy and a pathological outcome.

The next step was to investigate different methods of normalization. In current literature it is often unclear if and how normalization of the muscle EMG was applied and thereby it is difficult to compare study outcomes. We found that there are important differences between the methods of normalization. For instance: normalization is more effective if every individual trace is normalized instead of normalizing the averaged waveform (chapter 3.2). Using a trace by trace normalization it is also possible to use a longer period of time to collect the EMG information. In our study a trace-by-trace normalization of either RMS or rectified EMG over an as long as possible time window yielded the optimal results. If there are limited signal processing capacities available using the average pre-stimulus EMG is the normalization method of choice.

After proving the effect of normalization and evaluating the optimal method we further explored the use of cVEMP in patient groups. Using normalized cVEMP we explored the effect of cVEMP outcomes in Meniere's patients over time and compared this with outcomes in Vestibular Migraine patients. Over an average of 2 years the affected side of unilateral Meniere's patients had significantly worse cVEMP outcomes (both PP amplitude and threshold), while the unaffected side was stable (chapter 4). When we compared these outcomes to Vestibular Migraine patients, we found that the cVEMP outcome in this group was stable over a 2 year period in all patients. An important limitation of study was the retrospective design and the small number of patients. However each individual patient in the Meniere's group showed worsening of cVEMP threshold whereas each vestibular migraine patient showed stable thresholds. Given the study results, it would be useful to further investigate this prospectively. Since vestibular migraine is a relatively new diagnosis there are many patients in which the diagnosis (Meniere's vs. Vestibular migraine) is unclear. Since these uncertainties may take years to assess, it would be helpful to incorporate cVEMP's routinely in the evaluation of these patients and track them over time.

One of the critiques of cVEMP's is that they are difficult to complete, especially in older patients. By increasing the stimulation rate (i.e. the amount of tone bursts per second) we were able to reduce the test time by almost 40% without significantly altering the thres-

hold in healthy subjects (chapter 5). Studies showed that the peak-to-peak (PP) amplitude is affected by the stimulation rate: a higher rate yields lower PP amplitudes. Even though this is true, in our study the lower PP amplitudes did not result in a significant change in threshold, which was the main outcome measurement. This study was done in healthy, young subjects and it could be argued that in more senior subjects the increase of stimulation rate could result in altered outcome. In our clinic a stimulation rate of 13Hz is standard practice since many years and outcomes previously published were no different from other studies (although not many studies used threshold as an outcome measure).

The cVEMP is a relatively new test that might be a valuable addition to the vestibular testing battery, however it also poses challenges for the professionals that work with it. For audiologists a new test is emerging which requires skills to perform and interpret. For engineers it possess challenges in signal processing and response detection as is shown by the development of VEMP inhibition depth (VEMPid, see below). For the physician, in the field of ENT or neurology, the vestibular test battery grows. It is important to learn about these tests and their possibilities in order to implement and apply them correctly. What the clinical impact is for cVEMP is yet to be determined but many clinics already use the test as an aid in diagnosing Meniere's disease and superior canal dehiscence (SCD).

We believe there is a role for cVEMP testing in patients with Meniere's disease, vestibular migraine and superior canal dehiscence. In patients where it is unclear if they suffer from Meniere's disease or vestibular migraine, cVEMP seems to be able to aid in diagnosis if multiple test are performed over time. In our study we have shown that over time, the cVEMP in Meniere's patients worsen and in vestibular migraine patients this does not seem to happen, although this needs to be confirmed in a prospective study. For superior canal dehiscence, studies have shown that high frequency (2000Hz) cVEMPs are evoked with low thresholds, caused by the third window effect leaking acoustic energy to the vestibulum. In healthy subjects significantly higher thresholds are needed to elicit a response.

The studies presented in this thesis include mostly healthy young subjects because, to improve cVEMP testing, it is necessary to make these improvements using subjects in which there is little risk of influencing the outcome by subject characteristics or pathologies.

In conclusion this thesis describes a number of studies that have the common goal to make the

cVEMP more reliable, by applying normalization, and more feasible clinically by increasing stimulation rate. Also we describe the potential of the test to differentiate between clinically similar vestibulopathies (Meniere Disease and vestibular migraine).

Despite the improvements in cVEMP testing and analyzing there is still a lot of work to be done. Some of these challenges are discussed below.

The cVEMP mechanism

Evaluating the mechanism of cVEMP's was outside the focus of this thesis but is a part of VEMP's that is poorly understood. Current literature is focusing on this topic and recently a review by Curthoys was published in which a suggested physiology was described how the vestibular organ can be sensitive for a wide arrange of frequencies. Curthoys describes the classic accelerometer mode of operation in which the otoconia move relative to the macula (sensitive for slow movement) and a new "seismometer" mode in which the otoconia remain at rest which the macula is moving (for high frequency movements). This could be an explanation to how the balance organ is sensitive to high speed movements.

Development of new analyzing methods

Normalization is a way to reduce the effect of muscle contraction in cVEMP testing. The next step is to make the testing process more automatized as well. A new outcome measure for cVEMP has been described as VEMPid, the inhibition depth of the VEMP. This should more accurately produce the saccular function by estimating the percentage of saccular inhibition. This method uses a template correlation value, which is a number that describes how well a (cVEMP) waveform resembles the template. In order to calculate the VEMPid a template is needed to which the measured cVEMP can be compared, this can be a template recorded from the subject or a generic template (Noij et al. 2018). Using a generic template is especially important in testing patients in whom it is often difficult or impossible to record a proper cVEMP waveform (e.g. in bilateral Meniere's patients). Studies have shown VEMPid to be able to assess cVEMP threshold in healthy subjects and future studies must show if VEMPid can be used in vestibulopathies as well (Prakash et al).

What outcome to use?

In current literature there are different parameters described as outcome of the cVEMP. Early studies described a present/absent outcome at one frequency. This seems to be a relative crude outcome since previous studies have shown that the saccule's response to sound is frequency dependent. Therefore, similar to audiometry, it is important to test multiple frequencies. In Meniere's patients a tuning curve has been described in which the cVEMP threshold sensitivity changes over frequencies. Also, the cVEMP is not a present/absent response, it seems likely that when the saccule degrades the cVEMP response becomes more difficult to elicit (i.e. more stimulation is needed in order to evoke a response). Like an audiogram, the cVEMP seems to track a sliding scale and does not appear to be an "on/off" response. To adequately measure this scale, peak-to-peak amplitude or threshold would be a better outcome measurement. In chapter 4 we describe that threshold is sensitive to progressive disease in all tested frequencies (i.e. all frequencies worsen over time) whereas peak-to-peak amplitude is significantly different in half of the frequencies. The results of this study support our hypothesis that threshold seems to be the most informative outcome for clinical use. At Mass Eye and Ear cVEMP threshold, measured at multiple frequencies, is the main test outcome since many years. An example of a cVEMP outcome for a unilateral Meniere's patient is shown below.

VEMP Threshold (dB HL)

Freq. (Hz)	Right	Left
500	95	80
750	95	85
1000	95	85

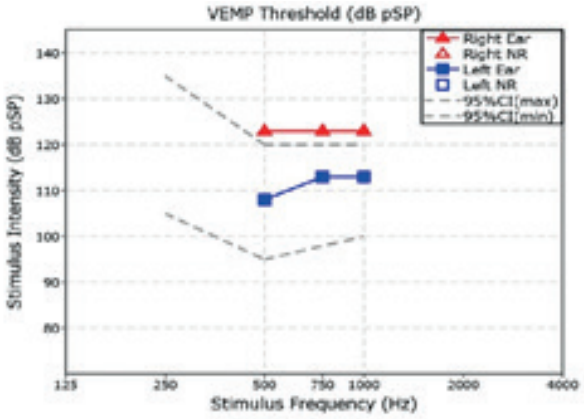

Figure 1. Example of the outcome figure of a cVEMP, a "VEMPogram".

Furthermore, in current literature the interaural asymmetry ratio (IAR) is an often used outcome measure. This outcome compares the PP amplitude from the healthy and the pathological side within a patient and gives a ratio as outcome. In a strictly unilateral disease this is a valua-

ble outcome, however in Meniere disease it is estimated that a third of the patients have (subclinical) bilateral disease. This means that the saccule can be affected on both sides but does not necessarily cause bilateral complaints. Separate studies have shown that about 30% of Meniere's patients' temporal bones show bilateral involvement. This number was also found in clinical studies and in our own cVEMP study we found that about of a third of the Meniere's patients diagnosed with unilateral Meniere's disease show increased cVEMP thresholds on the "unaffected" side. We do not yet know whether these patients will also develop bilateral disease, this is an important focus for future research. The contralateral affected cVEMP makes the IAR prone to under detection of Meniere's, therefore we recommend not to use this outcome in Meniere's patients. Future research will have to reveal which outcome is
most informative clinically.

Meniere's versus vestibular migraine

Vestibular migraine is a relatively new diagnosis. It is very likely that patients that have been diagnosed with Meniere's disease actually suffer from vestibular migraine. Especially in older literature it is important to keep this in mind and interpret results with caution. This is also true for VEMP testing, since our study suggests a different progression in time between these two pathologies. Even today it is sometimes difficult to differentiate clinically between the two. Since these uncertainties may take years to assess, it would be helpful to incorporate cVEMP's routinely in the evaluation of these patients and track them over time.

Effect of age on cVEMP

As described above and in current literature, the cVEMP is harder to elicit in older patients. In part this can be attributed to the difficulty of completing a cVEMP test, which takes a substantial amount of time and effort. Reducing test time and effort by increasing the stimulation rate and applying normalization could improve the ability to perform cVEMP in older patients. However the decline in vestibular function might also play an important role in this and could cause a higher amount of absent cVEMP responses in certain age groups, making the cVEMP less useful in these groups. However Meniere's disease, vestibular migraine and SCD usually have an age of onset at which the cVEMP is easy to elicit.

Standardizing

Since cVEMP testing is not standardized, it is necessary to specifically describe which variables are used for normalization. Applying adequate normalization methods has immediate clinical and research relevance. Our studies show the effect of normalization in a healthy, young population. Before standardizing cVEMP testing techniques it is important to assess how all outcome measures behave in pathological groups and across ages. This is already being done in current literature, however not always using optimal testing methods (i.e. the optimal normalization method). In order to make the cVEMP part of the regular "vestibular testing battery" it is important to investigate what is the optimal way of recording the response.

This thesis shows the effect of normalization in cVEMP and which method is most effective. Outcomes of the test will more adequately reflect the saccular function. Further research into developing more automated response recognition is already underway. Also the burden of the test could be reduced by increasing the stimulation rate. Future research will have to show the role of cVEMP in different vestibulopathies, but first we need to focus on developing a standardized method of testing.