Project Title:

Are test results from Subjective Visual Vertical and Ocular Vestibular Evoked Potentials correlated in a Danish Cohort of Patients admitted to a tertiary Dizziness Clinic?

AALBORG UNIVERSITY
STUDENT REPORT

REGION NORDJYLLAND
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Resumé

Formål: At undersøge hvorvidt der er overensstemmelse mellem oVEMP og SVV målinger i en heterogen gruppe af patienter, henvist med debuterende monosymptomatisk vertigo.
Metode: Et retrospektivt klinisk studie bestående af 103 patienter henvist til svimmelhedsambulatoriet på grund af debuterende monosymptomatisk vertigo. Samtlige patienter blev undersøgt med både SVV og oVEMP. De to tests blev sammenlignet ved hjælp af stratificering og Receiver Operation Characteristics (ROC) kurver, samt udregning af arealet under kurven (AUC).
Resultater: Når oVEMP antages at være referencepunkt for patologiske fund, viste et AUC [95%CI] på 0.83 for patienter med symptomvarighed på < 1 måned. ROC-kurver for den samlede studiepopulation, samt patienter med symptomvarighed > 1 måned, viste et AUC [95% CI] på < 0.5 indikerende dårligere overensstemmelse mellem SVV og oVEMP end den der kunne opnås ved ren tilfældighed. Patienter med Mb. Ménière, Neuritis Vestibularis eller BPPV blev stratificeret på baggrund af hvilken side den undersøgende læge angav som værende afficeret i patientjournalen. Resultaterne viste en overensstemmelse mellem lægelig vurdering og klinisk test på henholdsvis 27.5 % og 24 % for oVEMP og SVV. For patienter alene diagnosticeret med BPPV var der 20% overensstemmelse mellem lægelig vurdering og oVEMP såvel som SVV. Patienter der kun havde unilateral målbar oVEMP blev stratificeret i forhold til deres korresponderende SVV resultater. Dette viste en enighed på 34% mellem de to tests, samt at 59% af patienterne med normal SVV havde patologisk oVEMP.
Konklusion: Dette studie viste overensstemmelse mellem målinger fra oVEMP og SVV hos patienter med monosymptomatisk vertigo karakteriseret ved en symptomvarighed på under 1 måned. Til trods for at både oVEMP og SVV er en del af det vestibulære testbatteri og bidrager til det samlede billede bør man som klinikeer være meget bevidst om de relativt mange potentielle fejlkilder som disse undersøgelser besidder således de i fremtiden kan undgås eller minimeres.

Are test results from Subjective Visual Vertical and Ocular Vestibular Evoked Potentials correlated in a Danish Cohort of Patients admitted to a tertiary Dizziness Clinic?

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Abstract
Objectives: To investigate if any concordance exists between oVEMP and SVV results in a heterogeneous group of patients admitted with first time monosymptomatic vertigo. **Methods:** The retrospective clinical study included 103 patients referred to a tertiary dizziness clinic due to first time monosymptomatic vertigo. All patients were examined with SVV and oVEMP. The tests were compared by means of stratification as well as Receiver Operation Characteristics (ROC) curves with area under the curve (AUC) computed. **Results:** ROC curves comparing SVV and oVEMP results, with the oVEMP system as the benchmark for pathological findings, showed an AUC [95%CI] of 0.83 for patients with symptom duration of less than one month. The entire study population as well as the patients with symptom duration more than one month showed ROC curves with AUC [95%CI] of < 0.5 indicating less accuracy than random outcome. Patients with Ménière, Vestibular Neuritis or BPPV were stratified based on which side the examining doctor noted as being pathological. Pooled together, the three diagnoses demonstrated an agreement between the examining doctor and oVEMP or SVV of respectively 27.5% and 24%. An agreement of 20% was found for BPPV in regard to both tests. Patients with only one measurable oVEMP, stratified on SVV classification showed a 34% agreement between the two tests, as well as 59% of patients with normal SVV, but pathological oVEMP. **Conclusion**: Among patients experiencing monosymptomatic vertigo the present study showed a correlation between oVEMP and SVV results in patients with a symptom duration of less than one month. Despite oVEMP and SVV both being part of the extensive test battery in vestibular diagnostics, clinicians should be conscious of avoiding the potential errors discussed in this study; both during testing and interpretation.

Keywords: *otoliths, otolithic organs, utricle, dizziness, vertigo, SVV, subjective visual vertical, oVEMP, ocular vestibular evoked myogenic potential, central compensation*

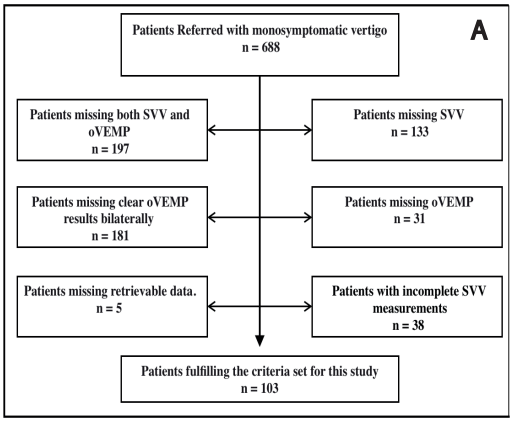
Introduction

The definition of vertigo, according to NHS's website, is "t*he sensation that you, or the environment around you, is moving or spinning*". A recent study, performed in Germany, showed that within the general adult population, ranging from 18-79 years old, people have a lifetime prevalence of 7.4% for experiencing vertigo[1]. Furthermore, it is one of the most common complaints in general practice in Denmark, accounting for up to 1-2% of all primary complaints, and substantially more frequent as a secondary or concomitant symptom[2].
Approximately 50% of patients presenting with monosymptomatic vertigo have inner ear pathologies. The vestibular portion of the inner ear consists of five paired organs; three semicircular canals (SCCs); inferior, superior,

and lateral, and two otolithic organs; the saccule and the utricle. The SCCs are responsible for detection of angular head movements in three different dimensions, while the otolithic organs are responsible for monitoring linear movements, such as gravity and linear acceleration. The saccule monitors vertical perception in the sagittal plane, e.g. linear acceleration, while the utricle monitors horizontal perception, e.g. the position of the head relative to gravity.
In patients with vertigo, the physician tries to locate the specific site of inner ear pathology. In recent years, there has been a huge leap in the diagnostic methods that evaluate inner ear function. Some of these methods enable diagnoses of pathologies located to the utricle(s).

Currently, two tests are used to examine the function of the utricles, which use vastly different approaches.
The Subjective Visual Vertical test (SVV) has been around since the early 1970's and has been suggested as a way of evaluating utricular function[3]. Originally, this test was based on a simple static method, using the subjective placement of a luminous rod[4]. However, in recent years this test has developed into more advanced types of SVV, including tilted SVV and unilateral centrifugation[5].
Briefly, when doing SVV, the patient is asked to position a rod in complete darkness as close to his/hers perceived verticality as possible. While doing so, the patient has to rely solely on the combined functions of the utricles to evaluate which position is vertical. Humans with normal vestibular function are able to do this within very narrow margins of errors, within only ±2 degrees of deviation[4,6–8]. It has been shown that people with reduced utricular function cannot determine verticality within the same margins as healthy people. This can be utilized diagnostically, since people presenting with vertigo as well as significantly abnormal SVV measurements most likely have a dysfunctioning utricle. Tilted SVV has been shown to increase the sensitivity of the test[9].

The second test, which has not been around for quite as long as SVV, is the ocular Vestibular Evoked Myogenic Potential (oVEMP). It is



B

Inclusion criteria

- First time visit due to monosymptomatic vertigo
- Vestibular test examinations including *both* oVEMP and SVV testing
- Characteristic oVEMP recordings containing clearly defined n10 and p15 peaks (figure 3B)
- oVEMPs with an action potential amplitude greater than baseline noise uni- or bilaterally
- SVV measurements with a minimum of three measurements at zero degrees without any single obvious outliers at every measured angle.

Exclusion criteria

- oVEMP action potential amplitudes smaller than or equal to baseline noise bilaterally.
- Missing oVEMP action potentials bilaterally.
- SVV report showing signs of overestimation (positive median SVV results during leftward head tilts OR negative median SVV results during rightward head tilts).
- Less than three SVV measurements at all measured head tilt angles (α)

C

oVEMP:

- A lack of acceptable and measurable action potential:
  - Missing characteristic looking n1-p1 action potential (figure 3B)
  - Missing action potential larger than the baseline noise
- In case of bilateral measurable action potentials, an asymmetry ratio >34% was considered pathological

SVV:

- If, at any given tilt-angle, the median of the angle of deviation (Δ) falls outside the confidence interval.
  - Positive Δ median = Right-sided pathology

Figure 1 - A) Trial Profile
B) Inclusion & exclusion criteria
C) Definition of pathology in oVEMP & SVV

still not fully concluded whether oVEMP examines the function of the utricle, the saccule, or both[10–22]. However, Kantner and Gürkov (2012) claim that the oVEMP most likely examines the function of the utricle[23]. Unlike the SVV, which involves higher cognitive assessment, oVEMP is based mainly on the function of the vestibular-ocular-reflex (VOR)[24]. The VOR is a reflex that results in a measurable myogenic potential formed at the

site of the inferior oblique muscle of the contralateral eye, when a patient's utricle is stimulated, usually by short bursts of sounds or vibration on the ipsilateral side[25,26]. A minor myogenic potential can also be measured on the ipsilateral side during stimulation. However, this is rarely used diagnostically, because this potential is inferior to the contralateral[24]. Hence, the VOR is a crossed as well as a bilateral reflex pathway[24,25]. Studies have shown that, in cases where there is an obstruction along the reflex pathway, for instance a dysfunctioning utricle, the myogenic potential produced from the inferior oblique muscle on the opposite side will be either reduced or absent dependent on the underlying pathology[27–29].

Since the aforementioned tests of utricular function are so different in their ways of assessing the utricular function, one being a dynamic test based on a reflex pathway whilst the other is considered a static test relying on the patients' subjective opinion of verticality, it is interesting to examine whether these two tests are correlated and if so, which of the two tests are more favorable in clinical practice, depending on the situation.

Valko et al.[30] examined the diagnostic value of roll-tilt SVV, UC-SVV and BC-oVEMP, in 11 patients with perceived peripheral vestibular hypofunction and 11 healthy subjects by means of comparison. The study showed that oVEMP and UC-SVV diagnose chronic unilateral vestibular hypofunction to a similar extent[30]. Angeli et al.[31] also did a study where they examined seven patients with both oVEMP and UC-SVV as a measure for utricular dysfunction, which also showed a correlation between oVEMP and UC-SVV results. Furthermore, Sun et al. recently examined the reliability of the so-called 'bucket test' version of SVV in a group of healthy subjects 70 y/o. The results of the bucket tests were compared to, among other tests, the asymmetry ratios obtained from tap-evoked oVEMPs. Though they only performed the SVV with the subjects at 0º (upright position), it showed a correlation between the oVEMP and SVV results nonetheless[32].
Nagai et al. also tested 22 patients with vestibular neuritis and 22 patients with Ménière, with both oVEMP and SVV at 0º. However, no significant correlations between SVV and oVEMP results in neither of the diseases were found, despite other studies showing a significant correlation between SVH(1) and oVEMPs in patients with Ménière[33,34].

As stated, only a few studies have compared oVEMP and SVV test results, showing conflicting results. To our knowledge it has not been examined to this extend. Therefore, this study seeks to compare the diagnostic value of sound-evoked oVEMP and tilt SVV via means of comparison in a larger population, to hopefully further clarify the reliability of both tests. In the light of this, our primary objective is to compare individual patients' oVEMP and SVV results to clarify a possible correlation. Hence, if a patient showed signs of unilateral pathology during one test, did the other test support the finding? Our secondary objectives are to investigate whether one of the tests detects certain diseases more frequently than the other test as well as to investigate whether the duration between time of debut of vertigo and the date of examination (duration of symptoms) has any influence on the tests results.

Purpose of the study

The purpose of this study was to examine if there is a significant correlation between SVV findings and recorded oVEMPs in patients admitted to a tertiary dizziness clinic due to monosymptomatic vertigo.

Material and methods

A retrospective study including patients, complaining of first time vertiginous

[1] Subjective Visual Horizontal is similar to SVV and Hafström *et al.* showed that the tests are "highly correlated"[58]

symptoms, referred to a tertiary dizziness clinic.

Patients/subjects

The initial search for eligible patients included a thorough review of patient records from January 2016 through November 2017. Initially, all first-time patients were included. The initial search revealed 688 patients examined at the dizziness clinic because of first time occurrences of vertigo during the inclusion period. 585 patients of these patients were excluded: 197 patients were excluded, because they missed both SVV and oVEMP tests, 133 patients were excluded, because they missed a SVV test, 181 patients were excluded, because they missed clear oVEMP results bilaterally (Figure 1B & 2B). 31 patients were excluded, because they missed an oVEMP test, 38 patients were excluded due to incomplete SVV measurements (Figure 1B), 5 patients were excluded, because it was not possible to retrieve the data (Figure 1A). The remaining 103 patients all met the inclusion criteria set for this study (Figure 1A). The patient group consisted of 38 males and 65 females with ages ranging from 12-87 and a mean age of 46.7 (16.6) (Table 1). Since the purpose of this study was to compare individual patients with themselves, there was no control group; hence the patients acted as their own controls and hence statistically the study is based on a comparison between matched populations. Of the 103 patients included, 5 patients were diagnosed with Ménière, 5 with Vestibular Neuritis, 32 with Benign Paroxysmal Positional Vertigo (BPPV), 18 with disruption of the sense of equilibrium(2), 5 with vertigo with disease classified elsewhere, 1 with benign tumors on the acoustic nerve (Schwannoma), 15 with a normal ENT examination, 4 with Migraine, 4 with labyrinthine fistulas, 2 with peripheral vestibular vertigo, 2 with labyrinthine hypofunction, 0 with otological disease causing vertigo, and lastly 10 patients were categorized as 'unspecified'(3)(Table 1).

Variable	Level	Total
age	mean (sd)	46.7 (16.6)
gender	male	38 (36.9)
	female	65 (63.1)
diagnosis	Ménière	5 (4.9)
	Vestibular Neuritis	5 (4.9)
	BPPV	32 (31.1)
	Disruption of the sense of equilibrium	18 (17.5)
	Vertigo with disease classified elsewhere	5 (4.9)
	Vestibular Schwannoma	1 (1.0)
	Unspecified	10 (9.7)
	Migrane	4 (3.9)
	Labyrinthine fistula	4 (3.9)
	Peripheral vestibular Vertigo	2 (1.9)
	Labyrinthine hypofunction	2 (1.9)
	Otological disease causing vertigo	0 (0.0)
	Normal ENT examination	15 (14.6)
measurable oVEMP	only right	21 (20.4)
	only left	11 (10.7)
	both	71 (68.9)
pathological (oVEMP)	none	65 (63.1)
	right	12 (11.7)
	left	26 (25.2)
asymmetry ratio > 34%	no	61 (84.7)
	yes	11 (15.3)
	missing	31
symptom duration	< 1 month	5 (4.9)
	1-3 months after debut	12 (11.7)
	3-6 months	14 (13.6)
	> 6 months	61 (59.2)
	unknown time of debut	11 (10.7)
no. of measures at -30 deg.	0	64 (62.1)
	1	0 (0.0)
	2	0 (0.0)
	3	1 (1.0)
	4	2 (1.9)
	5	36 (35.0)
no. of measures at -15 deg.	0	58 (56.3)
	2	0 (0.0)
	3	0 (0.0)
	4	1 (1.0)
	5	44 (42.7)
no. of measures at 0 deg.	2	0 (0.0)
	3	4 (3.9)
	4	4 (3.9)
	5	95 (92.2)
no. of measures at 15 deg.	0	57 (55.3)
	2	0 (0.0)
	3	0 (0.0)
	4	1 (1.0)
	5	45 (43.7)
no. of measures at 30 deg.	0	64 (62.1)
	2	0 (0.0)
	3	1 (1.0)
	4	1 (1.0)
	5	37 (35.9)
complete SVV	no	67 (65.0)
	yes	36 (35.0)
pat.m15	no	43 (95.6)
	yes	2 (4.4)
	error	0 (0.0)
	missing	58
pat.m30	no	32 (82.1)
	yes	7 (17.9)
	error	0 (0.0)
	missing	64
pat.0	no	71 (68.9)
	yes	32 (31.1)
	error	0 (0.0)
pat.p15	no	45 (97.8)
	yes	1 (2.2)
	error	0 (0.0)
	missing	57
pat.p30	no	37 (94.9)
	yes	2 (5.1)
	error	0 (0.0)
	missing	64
pathological (SVV)	none	64 (62.1)
	right	14 (13.6)
	left	25 (24.3)

Table 1 - Background characteristics.
Complete SVV = Five measurements at each of the five tilt-angles (+30°, +15°, 0°,-15°,-30°).
Pat.m15 = Pathological SVV measurements at -15°
Pat.m30 = Pathological SVV measurements at -30°
Pat.0= Pathological SVV measurements at 0°
Pat.p15 = Pathological SVV measurements at +15°
Pat.p30 = Pathological SVV measurements at +30°

[2] Disruption of sense of equilibrium is usually given to patients who might have vestibular migrane, or who at the time of examination doesn't indicate vestibular malfunction as the cause of their symptoms.

[3] All diagnoses which do not include the aforementioned diagnoses.

Ocular Vestibular Evoked Myogenic Potential

For oVEMP-testing the patients were seated upright on a chair for the duration of the test. Two sets of silver chloride electrodes were placed below each of the patient's eyelids. One set of electrodes were the active electrodes, which are placed as close to the inferior eyelid as possible, approximately 1cm infraorbitally. The other set of electrode, referred to as the reference set, was placed on the chin. A ground electrode was then placed on another part of the body, most commonly the forehead (FPz/Fz). The patient was asked to wear a set of insert headphones, through which the VOR would be stimulated (Figure 2D).

The patients were asked to maintain an upwards gaze at an angle of 30 degrees for the duration of the testing, since this has shown to produce the greatest action potential[35–37].

The VOR was stimulated using a series of 500 click tone-bursts at a rate of 5 Hz, in a 2-0-2 cycle at a frequency of 500 Hz, at an intensity of 100 dB nHL. The series of air-conducted stimuli were measured below the contralateral eye, because the crossed pathway of the VOR shows a greater amplitude[24]. Following this, the electromyogenic potentials undergo amplification and the bandwidth filtered. These measurements are then averaged to give the final response curve. The response curve has a characteristic appearance, with an initial negative peak (n1) occurring at a latency of approximately 10ms, followed by a positive peak (p1) occurring at a latency of approximately 15ms (Figure 2B).

The final response curve was then analyzed using the VEMP-module from the Interacoustics Eclipse®. The clinician manually plots in n1, p1, from which the n1-p1, peak-to-peak amplitude and asymmetry ratio is then calculated.

Subjective Visual Vertical

Patients in this study were tested and managed using the Virtual SVV™ software from Interacoustics.

All the subjects were examined by means of SVV. 36 patients were examined with five measurements at each of the five tilt-angles (+30°, +15°, 0°, -15°, -30°), considered in the respective clinic as a complete SVV test. 56 patients had only been examined at tilt-angle 0° degrees (Table 1).

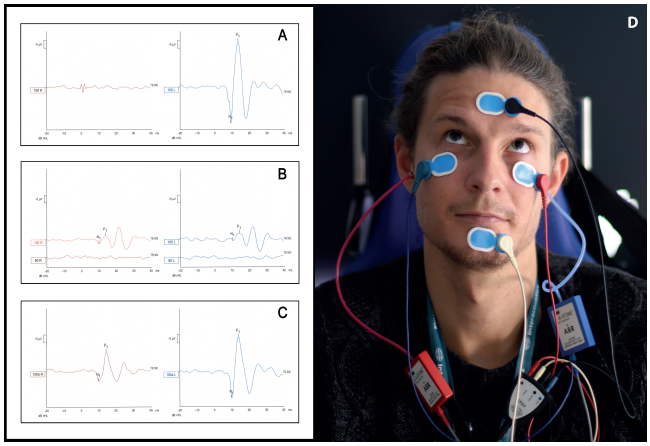


Figure 2 – oVEMP testing. Red indicates right side measurements and blue indicates left side measurements. True oVEMP potentials have a negative deflection (n1) at 10ms and a positive deflection (p1) at 15ms.
A) Pathological oVEMP, with missing characteristic configuration on the right side. Normal oVEMP on the left side.
B) Normal characteristic oVEMP bilaterally.
C) Pathological oVEMP, with reduced amplitude but yet characteristic configuration on the right side. Normal oVEMP on the left side. AR>34%
D) oVEMP test setup - note the insert headphones, two active electrodes suborbitally, a reference electrode placed on the chin and a ground electrode placed on the forehead. Also, note the patient's upward gaze of the eyes during testing.

During the test, patients were seated upright while wearing a pair of goggles, which totally deprived the patients visual field from any fixation points and gravitational cues. Inside the goggles a screen was located in front of the eyes, which showed a luminous rod. Preceding each measurement, the rod was positioned at a, by the accompanying software, random angle. Then the patient was asked to rotate the luminous rod to the position perceived by the patient as vertical, by using a joystick (Figure 3). The data was simultaneously managed by using the Virtual SVV™ software, which enabled the examiner to follow what the patient was presented with inside the goggles. The software also allows monitoring of the patient's head-tilt-angle via the computer (Figure 3). The different tilt-angles were obtained by asking the patient to actively hold their head in the desired tilt-angle position. In

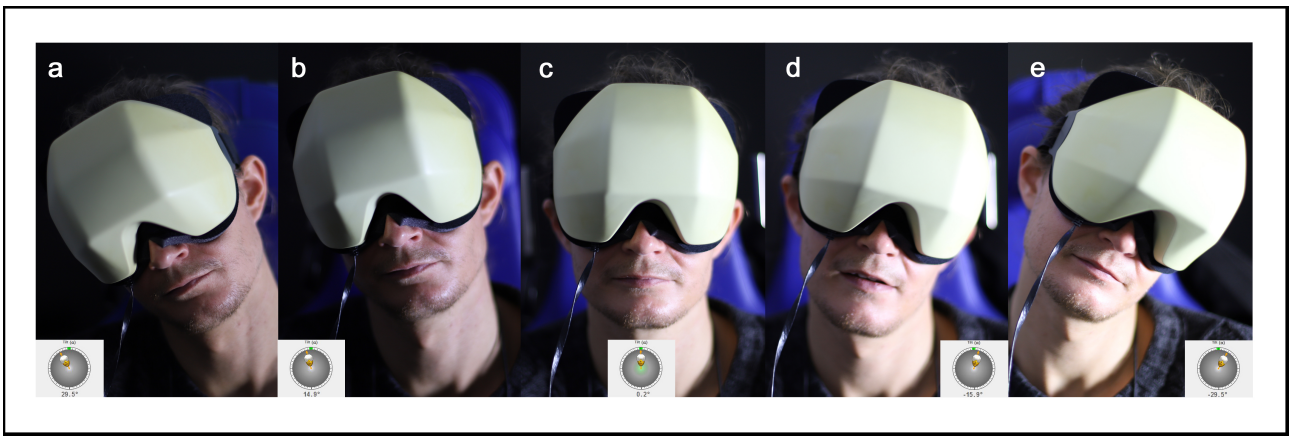


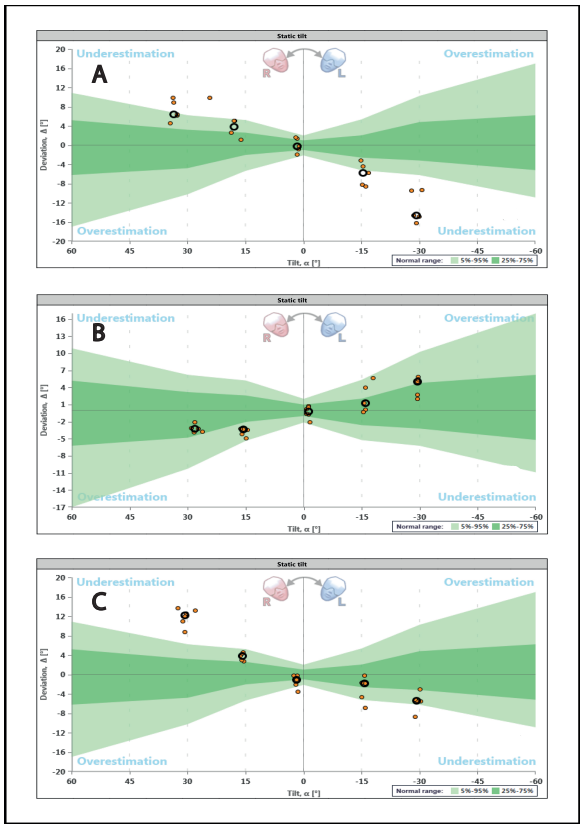
Figure 3 - Patient wearing SVV goggles at all five test angles: a) +30, b) +15, c) 0, d) -15, e) -30. Because the test goggle is firmly fitted a test environment in complete darkness without any reference points is created.
Note indicator of test angle (α) in the lower right corner, enabling the clinician to monitor the patient's test angle.

order to ensure the tilt-angle was correct and maintained throughout the test, the clinician continuously followed the Virtual SVV™ software interface and directed the patient.

Statistical testing

For oVEMP-testing, the peak-to-peak values as well as the latency duration were calculated by subtracting the amplitude and the latency of p1 from n1. Furthermore, the asymmetry ratio (AR) was calculated using Jongkees formula: AR = {(larger peak-to-peak amplitude - smaller peak-to-peak amplitude)/(larger peak-to-peak amplitude + smaller peak-to-peak amplitude)} x 100.
oVEMPs were categorized as pathological/abnormal when certain action potentials with characteristic appearances could not be recorded and when small action potential amplitudes did not allow for discrimination between baseline noise and recorded signal (Figure 2A). In patients where two oVEMPs were measured, ARs larger than 34% were concluded as being abnormal/pathological, whilst the side displaying the smallest peak-to-peak amplitude was categorized as the site of the pathology (Figure 2C). The AR cut-off value was based on a study performed by Piker et al., which showed a similar oVEMP setup as ours[38].

For SVV-testing, the angle of the head-tilt was defined as "α". SVV was defined as "β". The Angle of deviation was defined as "Δ" and is the difference between the SVV and the head's tilt-angle, following the formula "Angle of



D	0	15	30	-15	-30
lower ci	-2.1	-5.4	-10.6	-5.3	-5.9
upper ci	2.0	5.3	6.2	5.4	10.6

Figure 4 - Different SVV measurements & confidence interval.
A) Pathological SVV measurements with a median underestimation at -15 and -30, indicative of a left-sided pathology.
B) Normal SVV measurements, all medians are within the range of the confidence interval.
C) Pathological SVV measurements with a median underestimation at +30, indicative of a right-sided pathology
D) Confidence interval used to detect the normal range for the SVV system, obtained from SCHÖNFELD and CLARKE[5].

Deviation (Δ) = SVV Angle + Angle of Head Tilt". The median was calculated based on the five measured -values, as well as the five measured α (one for each head-tilt position). The angle to the corresponding median measure was used to calculate the exact confidence limits using linear interpolation from confidence limits shown in figure 4D, which was based on normative data established by UWE et al.[5]. If only four measures were available, an average was instead used of the two middle measures, and likewise the angle was calculated as the average of the corresponding angles. Previous findings by

Vibert, Hausler and Safran (1999) have suggested that a unilateral utricular deficit will result in the SVV deviating towards the pathological side[5,39]. Hence, a positive Δ median, which fell outside the 5th-95th-percentile threshold, is representative of pathology in the right utricle, while a negative Δ median, which fell outside the 5th-95th-percentile threshold, is indicative of pathology in the left utricle.

Sensitivity and specificity of the SVV system were calculated, when considering results of the oVEMP system as the true results. These were presented as Receiver Operating Characteristic (ROC) curves, and the area under the curve (AUC) was computed. Subanalyses were made on patients with different time intervals from debuting symptoms.

For the calculations of sensitivity and specificity, a detection of a right pathology by the SVV system was considered as a false negative when it was detected as a left pathology by the oVEMP system and vice versa.

Results

Descriptive statistics showed that out of the 103 patients included in the study, 64 patients produced normal SVVs, 25 patients had SVVs indicating left-sided pathology and 14 patients had SVVs indicating right-sided pathology,

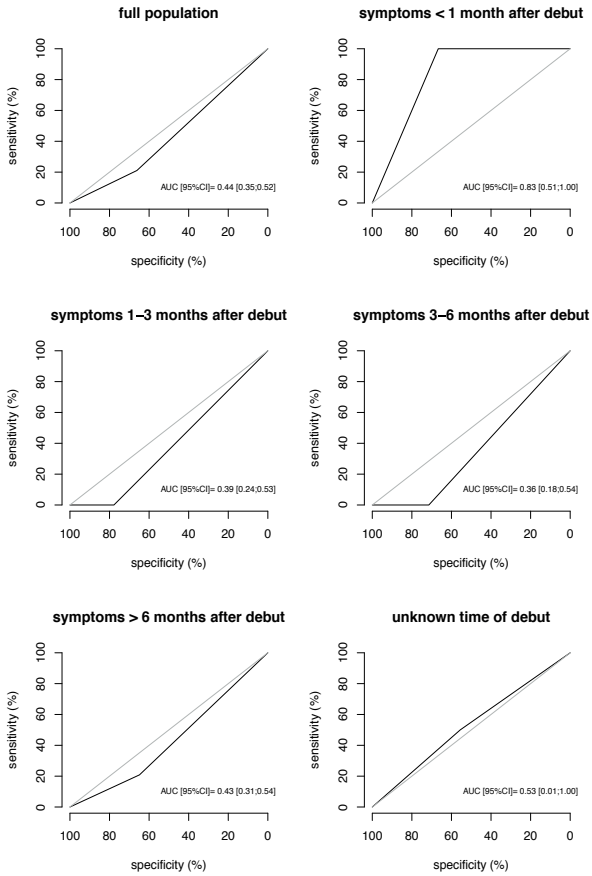


Table 2 - Receiver Operation Characteristics (ROC) curves. The sensitivity describes the true positive rate of the SVV system, when results of the OVEMP system defines true pathological. The area under the black curve defines "The Area Under the Curve (AUC)". The grey line indicates where the results of the SVV system would be random compared to results of the OVEMP system, corresponding to AUC=0.5.

accounting for 62.1%, 24.3%, and 13.6% of the overall study population, respectively (Table 1).
Out of 103 patients, 65 patients produced normal oVEMPs, 26 patients had oVEMPs indicating left-sided pathology and 12 patients had oVEMPs indicating right-sided pathology, accounting for 63.1%, 25.2%, and 11.7% of the overall study population, respectively (Table 1).

ROC curves were calculated with the oVEMP system as the benchmark for pathological findings. When comparing the entire study population with SVV, an AUC [95%CI] of 0.48 was found, indicating that the SVV is less accurate than a random outcome (Table 2). ROC curves were also made with the study population divided into five subgroups based

on the duration of vertiginous symptoms preceding date of examination. This revealed an AUC [95%CI] of 0.83 for the group with duration of symptoms less than one month. The remaining groups (symptom duration of 1-3 months, 3-6 months, and > 6 months) all showed AUC [95%CI] < 0.5 indicating less accuracy than a random outcome. The group 'unknown time of debut' had an AUC [95%CI] of 0.53 (Table 2).

Patients who received a diagnosis of either Ménière, Vestibular Neuritis or BPPV underwent stratification based upon which side the examining doctor had noted as being pathological; the information obtained from the patient report. The stratified table shows an agreement of 8 out of 29 for oVEMP and 7 out of 29 for SVV, not counting the 'missing'-group, corresponding to agreements of approximately 27.5% and 24% respectively (Table 3A).

A

Variable	Level	left (n=18)	right (n=11)	Missing (n=13)	Total (n=42)
ovemp	none	11 (61.1)	7 (63.6)	5 (38.5)	23 (54.8)
	right	0 (0.0)	1 (9.1)	3 (23.1)	4 (9.5)
	left	7 (38.9)	3 (27.3)	5 (38.5)	15 (35.7)
svv	none	11 (61.1)	5 (45.5)	10 (76.9)	26 (61.9)
	right	2 (11.1)	2 (18.2)	1 (7.7)	5 (11.9)
	left	5 (27.8)	4 (36.4)	2 (15.4)	11 (26.2)

B

Variable	Level	left (n=12)	right (n=8)	Missing (n=12)	Total (n=32)
ovemp	none	8 (66.7)	5 (62.5)	4 (33.3)	17 (53.1)
	right	0 (0.0)	0 (0.0)	3 (25.0)	3 (9.4)
	left	4 (33.3)	3 (37.5)	5 (41.7)	12 (37.5)
svv	none	6 (50.0)	5 (62.5)	9 (75.0)	20 (62.5)
	right	2 (16.7)	0 (0.0)	1 (8.3)	3 (9.4)
	left	4 (33.3)	3 (37.5)	2 (16.7)	9 (28.1)

Table 3:
A) patients with either Ménière, Vestibular Neuritis, or BPPV. Stratified according to doctor's classification of side of pathology.
B) patients with BPPV. Stratified according to doctor's classification of side of pathology.
The group 'Missing' includes patients where the doctors could not determine the side of pathology.

The same stratified tables were produced with BPPV patients. In this case an agreement of 20% (4 out of 20 excluding the missing group) was found between the clinical estimate performed by doctors and both oVEMP and SVV (Table 3B). However, results also showed a 15% (3 out of 20 excluding the missing group) and 25% (5 out of 20 excluding the missing group) disagreement between the clinical estimate performed by doctors and oVEMP and SVV respectively.

Another stratified table was made comparing patients with only unilateral oVEMPs to SVV classification, thereby excluding patients with normal oVEMPs and those with an AR above 34% (Table 4). The stratified table shows an agreement between the two tests in 11 out of 32 patients (approximately 34%). However, 19 out of 32 patients showed pathological oVEMP results whilst SVV showed no sign of pathology, this group accounts for approximately 59%. Furthermore, the table shows that 2 out of 32 patients (6.25%) exhibit left-sided pathological measurements on SVV, but right-sided pathological measurements on oVEMP (Table 4).
Lastly, a subanalysis was made to give an overview of the characteristics of the 19 patients displaying normal SVV and concomitant pathological oVEMP (Table 4). Within this group, zero patients had symptom duration of less than one month before testing, two patients (10.5%) had symptom duration of 1-3 months before testing, four patients (21.1%) had symptom duration of 3-6 months before testing, 12 patients (63%) had symptom duration of more than 6 months before testing, and one patient had symptoms for an unknown amount of time between symptom debut and testing.

Variable	Level	none (n=19)	right (n=3)	left (n=10)	Total (n=32)
ovemp	none	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	right	6 (31.6)	3 (100.0)	2 (20.0)	11 (34.4)
	left	13 (68.4)	0 (0.0)	8 (80.0)	21 (65.6)
symptom duration	< 1 month	0 (0.0)	1 (33.3)	1 (10.0)	2 (6.2)
	1-3 months after debut	2 (10.5)	0 (0.0)	0 (0.0)	2 (6.2)
	3-6 months	4 (21.1)	0 (0.0)	1 (10.0)	5 (15.6)
	> 6 months	12 (63.2)	1 (33.3)	8 (80.0)	21 (65.6)
	unknown time of debut	1 (5.3)	1 (33.3)	0 (0.0)	2 (6.2)

Table 4 - Patients with only one measurable oVEMP. Stratification based upon SVV classification. Sub-analysis with duration of vertiginous symptoms.

Discussion

Current research regarding oVEMP and SVV shows there is no consensus yet regarding what end-organ the two tests examine, especially the oVEMP. Several studies indicate that oVEMP

most likely examines the superior vestibular nerves and hence mainly the utricles[10-16,20-22]. However, other studies indicate that oVEMP examines the saccules or even both otoliths[17–19].
In this study, we assumed that both tests examine the function of the superior vestibular nerve and specifically the utricule. Presently, discussions are still ongoing about the specificity between stimulation mode (bone conducted stimuli versus air conducted stimuli)[40] and end-organ activation (saccule versus utricle). A thorough explanation and analysis of these are beyond the scope of the present study.

Is there a correlation between SVV results and oVEMP results in patients admitted to a tertiary out-patient clinic with monosymptomatic dizziness?

oVEMP is relatively new and therefore comparisons with other tests are limited. Lin et al.[34] compared SVH, oVEMP and cVEMP in 20 healthy subjects and 20 patients with unilateral Ménière. The study showed a significant correlation between the test results from SVH and oVEMP, in both the healthy subjects and Ménière patients[34]. As mentioned earlier, other studies have also shown a correlation between oVEMP and SVV, though this was not the main purpose of those studies[30–32,34]. On the other hand, Noriko et al. found no significant correlation between SVV and oVEMP results[33].

In this study, no correlation was found between SVV and oVEMP for the entire patient group, which is in contrast to the majority of aforementioned research. However, when dividing the study population into subgroups based upon symptom duration, there was a correlation between the two tests in the subgroup of patients with symptom duration of less than one month, which included only five patients. All patients with symptom duration exceeding one month showed poorer specificity than random outcome (Table 2).

This is in agreement with previous studies which showed that patients with chronic vestibular dysfunction often have normal SVV results[3,6].

Considering the basis, method and analysis of the two tests, as well as the restrictions of the study setup, the contradictory results might be explained by several factors, which will be discussed in the following sections.

Unlike oVEMP, SVV is subject to gradual normalization over time after the initial symptom debut, presumably in large part due to central compensation[3,6,29,41,42]. In this study, concordance between the two tests was found, but only in patients with a symptom duration of less than one month. This finding makes it plausible that patients with pathological oVEMP and normal SVV have undergone a high degree of central compensation. Because the present study is done retrospectively, symptom duration was difficult to determine for all patients exactly and had to be estimated in some cases, based upon information concealed in the patient records. Therefore, under- or overestimations of symptom duration might have occurred.

According to the manufacturer of the Virtual SVV™ used in this study as well as a number of previous studies, performing the SVV at tilted angles increases the sensitivity of the test by prolonging the duration of time before central compensation normalizes results[9]. Studies have shown that the SVV deviation increased as patients tilted their head towards the pathological ear[43–45] and therefore a complete SVV examination is preferred. Patients that have not been examined completely, but only at 0 degrees, possibly represent an underestimation of pathological SVVs in this study.

Furthermore, several factors have been shown to affect the stimulation of the utricle and thereby the amplitude of the action potential measured during oVEMP. Factors such as age[12], skull characteristics[46], muscle mass[12],

gender[12], conductive hearing loss[47–49], electrode placement[50] and stimulation frequency[51] can influence the test results. For instance, several studies show that oVEMP amplitudes significantly decrease with age, which can lead to bilaterally missing action potentials[38,52–55]. Also, several studies showed that even slight conductive hearing loss can result in significantly reduced oVEMP amplitudes, which might lead to false positives[47–49]. Sometimes, patients lack the ability or motivation to maintain the upwards gaze needed for the full duration of the test, which causes compliance issues. In this study, it was not possible to consider all these factors individually, which might have resulted in false positive oVEMPs. All tests were performed by four different clinicians, which decreases reliability due to interpersonal variation[56].

The large variation in oVEMP peak-to-peak amplitudes make interpersonal comparisons of measurements difficult. Since oVEMP tests each utricle individually, it is possible to use the AR to evaluate pathologies by comparing the results produced by both ears of the individual patient. However, studies show that the AR normative values also vary greatly, so a standard cut-off value dictating pathology has yet to be defined[12]. It is advised that each institution collect data to estimate local normative data as well as cut-off values. Since these were not available at the time of this study, normative values from Piker et al. were used, because they used a similar setup[38]. This should be taken into account when interpreting the results, since overestimating the AR cut-off value would result in an underrepresentation of pathological oVEMP measurements and vice versa.

SVV is a 'subjective' evaluation based upon the joined sum of information from different systems, which increases the risk of bias. The test also requires more cooperation from the patient in comparison to oVEMP. SVV requires thorough explanation, since the results to a greater degree depend on the patient's cooperation. This might potentially lead to patients misunderstanding how to perform the test and as a consequence might lead to unreliable results. For instance, it seems that some patients might think that the luminous bar should be placed at 0º in relation to their head tilt, as opposed to gravity. Lack of familiarity with the concept of a joystick, e.g. among elderly patients, could hamper the test. Lastly, SVV at our clinic is often performed as the last test of a series of quite time consuming and demanding vestibular tests; all factors that could reduce patient compliance. It should be noted that due to the setup of the test, the head-tilts are rarely maintained at the specific angles for the duration of the test, since the patient has to actively hold their head in place. Also, there seems to be no calibration system equipped to the SVV-goggles. One can assume that, if the clinician does not have a way of assessing whether the SVV-goggles are positioned horizontally, it might result in a substantial deviation of measurements, especially when measuring in 'upright'-position due to the narrow confidence interval at this angle (± 2 degrees)[4,6–8]. This might account for some of the SVV measurements showing disagreement with corresponding oVEMP results. Based on the majority of the literature on the subject one would assume that whilst there might be patients with pathological oVEMPs but normal SVV, the opposite should only rarely be true. Certain issues should be considered when interpreting the results. The normative data used to produce our confidence interval had only been examined at specific tilt-angles (0º, ±15º, ±30º), though as mentioned patients rarely were examined at exactly these angles. Furthermore, the confidence interval between the tilt-angles were interpolated, they might therefore not fully reflect reality. Lastly, it is plausible that the inclusion criteria of the study were too restrictive, since all patients showing signs of overestimation were excluded (Figure 1B). The purpose was to set 'clear' definitions of unilateral pathology, though less restrictive criteria are used in the clinic (Figure 1C). This could possibly result in lesser numbers of

patients with unilateral pathologies being included, thereby reducing the power of the results.

Knowing that Ménière, Vestibular Neuritis and BPPV are diseases that often cause unilateral vestibular disease, all three diseases were stratified based on the clinical estimate performed by doctors. Since BPPV is the most common vestibular cause of vertigo and the most common diagnosis in our patient group, this diagnosis alone was also internally stratified based upon the clinical estimate performed by doctors[57] (Table 3A & 3B).
When all three diagnoses were pooled together, oVEMP seemed to correlate marginally better than SVV to the clinical estimate performed by the doctor. When looking at BPPV alone, there was no difference in agreement between the two tests. However, oVEMP showed 15% disagreement, whilst SVV showed 25% disagreement, with the clinical estimate performed by the doctors. These disagreements might partly be due to a unilateral conductive hearing loss or the fact that not all patients with BPPV seem to have a dysfunctioning utricle.
The 'missing'-group included patients where the examining doctor had either not clearly stated one side as being pathological or patients where the diagnostic criteria for the given diagnosis were not fully met. This group accounts for approximately 31% of the patients in the pooled group and 37.5% of the BPPV patients (Table 3). Secondly, in more than 55% of the cases no pathology was found with either oVEMP or SVV, despite the examining doctor applying a unilateral diagnosis. Presumably, in the case of SVV, it can be explained partly by central compensation. Also, some of the patient's vertiginous symptoms, might not be due to utricular dysfunction.
Based on the previous arguments one would assume that the patients with unilateral utricular dysfunction have corresponding missing oVEMPs or significant AR. However, as discussed, many factors might account for the somewhat contradicting findings.

Lastly, it was hypothesized that patients who produced one measurable oVEMP would have the most severe pathologies. Therefore, patients with normal oVEMP bilaterally or an AR above 34% were excluded and the remaining patients were compared to their individual SVV result by means of stratification and sub analyzed by symptom duration. The results show approximately 34% agreement and a 6.25% disagreement between the two tests. Furthermore, approximately 54% of the patients had pathological oVEMP results whilst having normal SVV results. All these patients also had symptom durations exceeding one month, which indicates that it might be due to central compensation (Table 4).
Thus, at least in severe cases with symptom duration of less than one month, there seems to be a correlation between oVEMP and SVV results.

Despite these tests being used to access utricular function, it is clear that a dysfunctioning utricle is not the only cause of a pathological/abnormal oVEMP or SVV reading/measurement.
The oVEMP, as mentioned earlier, utilizes the VOR, which results in a measurable action potential suborbitally on the contralateral side in healthy individuals[25,26]. However, due to the course of the VOR, damage to the vestibular nerve, the brainstem, the oculomotor nerve or the inferior oblique muscle itself can result in an absent measurable action potential during oVEMP testing[24]. In contrast to oVEMP, SVV relies upon a combination of information from the inner ear, the visual system, proprioception and higher cognitive assessments, which also allows other factors than a dysfunctioning utricle to result in abnormal SVV measurements. All of this must be taken into account when interpreting the test results.

Conclusion

The results of the study have found a concordance between oVEMP and SVV results from vertiginous patients with symptom duration of less than one month. However, no concordance between oVEMP and SVV was found within the entire patient group or in patients with symptom duration longer than one month. When test results from patients

with Ménière, Vestibular Neuritis or BPPV were compared to the clinical estimate performed by doctors, both tests showed poor correlation, though oVEMP showed slightly better correlation than SVV. Lastly, when comparing patients displaying only unilateral oVEMPs with the SVV of the individual patient, the study showed good correlation between the two tests, when taking into account the large group of patients with normal SVV despite pathological oVEMPs. Though neither SVV nor oVEMP be stand-alone tests, diagnostically they can significantly contribute to the overall picture. Especially in combination with a full vestibular examination (caloric test, v-HIT, c-VEMP and clinical evaluation). However, it is important that the otoneurologist is aware of the potential sources of errors of both SVV and oVEMP both during testing and the following interpretation.

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