

ORIGINAL ARTICLE

## Evidence of unilateral isolated utricular hypofunction

UWE SCHÖNFELD<sup>1</sup>, KAI HELLING<sup>2</sup> & ANDREW H. CLARKE<sup>1</sup>

<sup>1</sup>Department of Otorhinolaryngology, Charité, University Medicine Berlin, Berlin and <sup>2</sup>Department of Otorhinolaryngology, Johannes Gutenberg University Medical School, Mainz, Germany

### Abstract

**Conclusions:** The findings demonstrate that an enduring unilateral utricular dysfunction, possibly together with canal hypofunction, can occur after labyrinthine disease or injury. They also suggest that unilateral, isolated utricular dysfunction – or utricle paresis – can occur, representing a novel entity in the differential diagnosis of peripheral vestibular function. The occurrence of subjective visual vertical (SVV) asymmetry in the presence of symmetric vestibular evoked myogenic potentials (VEMPs) also confirms that the information from the utricles, rather than the saccules, dominates SVV estimation. **Objectives:** To determine the incidence of unilateral utricular hypofunction. **Methods:** The retrospective clinical study deals with a selection of those vestibular patients who showed pathological responses to utricle testing. Peripheral vestibular function was examined in a group of 110 patients. Utricular function was evaluated by estimation of SVV during unilateral centrifugation. Bithermal caloric testing was performed to assess unilateral semicircular canal function. Saccular function was tested by measurement of VEMPs. **Results:** A total of 46 patients were found with asymmetric SVV findings ( $p < 0.001$  for healthy versus lesioned ear), but symmetric caloric responses and VEMPs. Statistical testing also verified that their SVV asymmetry factors were significantly higher than those calculated for caloric responses and VEMPs ( $p < 0.001$ ).

**Keywords:** Otolith dysfunction, utricle, unilateral centrifugation, subjective visual vertical, peripheral vestibular lesion, utricle paresis

### Introduction

Differential diagnosis of labyrinth function has undergone substantial improvements over the last few decades. In particular, we are now in a position to examine the function of each otolith receptor. The measurement of vestibular evoked myogenic potentials (VEMPs), introduced by Colebatch et al. [1], permits unilateral testing of saccular function, and the unilateral centrifugation (UC) technique [2] provides a means for examining unilateral utricular function, either by measuring the otolith-ocular responses [3,4] or the subjective visual vertical (SVV) [5]. The possibility of measuring oculomotor responses to acoustic clicks [6] and more recently, of obtaining evoked potentials from the extraocular muscles [7], promises additional inroads for the evaluation of otolith function, arguably of the utriculo-ocular pathways.

In many cases, in which sensations of dizziness with tilt illusions and postural instability are reported but caloric testing proves normal, peripheral disorder is ruled out. This argument is questionable. Numerous reports on clinical testing of the SVV, i.e. of otolith function, indicate involvement of the otolith organs in the acute phase of peripheral vestibular dysfunction [8,9]. However, lacking clinical evidence, the prevalence of unilateral otolith disorders has remained unclear to date. The present retrospective clinical study deals with a selection of patients who showed pathological responses to unilateral utricle testing. It is based on the measurement of SVV during UC stimulation and addresses the question as to whether unilateral isolated utricular dysfunction – or utricle paresis – can occur. This would represent a novel category of peripheral vestibular dysfunction. In a previous report Clarke et al. [10] reported on their

first observations of a singular loss of utricular function.

## Material and methods

### Patients

Unilateral otolith function testing has been performed with a total of 538 patients at the Charité dizziness clinic over the period 2003–2008. In 69% of these patients, among other findings, an asymmetry in SVV estimation during UC was observed. However, the present analysis only considered those patients who had been subjected to routine vestibular testing in our own vestibular lab and for whom full test records were available. Those referred from other clinics or institutions for additional otolith testing were excluded, as their files were either unavailable or incomplete. Accordingly, those patients included in the present analysis ( $n = 110$ ) had undergone extended examination of unilateral semicircular canal (SCC) with bithermal caloric responses and rotatory chair testing, and unilateral otolith function with VEMP measurement and SVV estimation during UC. All told, asymmetric SVV estimation (with or without symmetric caloric responses and VEMPs) during UC was observed in 74% of these patients, i.e. a comparable percentage to that observed in the total population examined ( $n = 538$ ).

In many cases the head impulse test had been performed during initial screening, but this was not systematically documented. Accordingly, the preconditions for classification as isolated, unilateral utricular hypofunction were the presence of asymmetric SVV estimates together with symmetric caloric responses, indicating normal SCC function, and symmetric VEMP responses indicating normal saccular function. Further, all patients included proved negative in the Dix-Hallpike test for acute benign paroxysmal positional vertigo (BPPV). In total, 46 such cases with presumed isolated unilateral utricular dysfunction were identified. In the following, the designation of healthy and lesioned ear was made on the basis of the unilateral SVV findings of each individual.

The preliminary diagnoses of all patients were classified as follows. *Otolith dysfunction*: no identifiable cause, mainly postural and locomotor instability, seldom reports of nausea. *Acute peripheral vestibular dysfunction*: repeated occurrences of sudden vertigo attacks, often with nausea. BPPV excluded. *Post-traumatic vertigo*: accident with head trauma. *BPPV*: diagnosis of intractable BPPV. *Gentamicin toxicity*: transtympanic application as therapy for Ménière's disease.

### Caloric testing

Caloric testing was performed using a standardized sequence of 30 s irrigations with 100 ml of water (44°C right ear, 44°C left ear, 30°C left ear, 30°C right ear). Nystagmus activity was recorded throughout by DC electro-oculography (EOG) and the slow phase velocity (SPV) was calculated. The culmination SPVs from the four irrigations (extracted from the interval 30–60 s after stimulation) were used to determine the response intensity of the lesioned and healthy ear and the resulting asymmetry factor:

$$\frac{|(44^\circ\text{C} + 30^\circ\text{C})_{\text{healthy}}| - |(44^\circ\text{C} + 30^\circ\text{C})_{\text{lesion}}|}{|(44^\circ\text{C} + 30^\circ\text{C})_{\text{healthy}}| + |(44^\circ\text{C} + 30^\circ\text{C})_{\text{lesion}}|} \times 100$$

Values <25% were classified as normal.

### VEMP testing

Saccular function was tested by measurement of VEMPs. EMG activity was recorded from symmetrical sites on the upper half of each sternocleidomastoid muscle (SCM), a reference electrode on the upper part of the sternum and a ground electrode on the forehead. During the measurements the test subject was supine and was required to raise and hold his/her head in order to tension the SCM muscle. The acoustic stimuli (click stimuli, 0.25ms; rarefaction, 5/s) were presented via calibrated headphones (Beyer DT48). For averaging, the EMG signal was extracted over the interval from 20 ms pre- to 100 ms post-click stimulus and normalized to the RMS (root mean square) value of the EMG activity over that interval; 150 EMG signal extracts were averaged for each trial. Stimulus intensities of 135 to maximum 145 dB (SPL) were employed. The normalized amplitudes and symmetries of the patients' responses were compared to those of a normal control group ( $n = 43$ ). The result was classified as normal if the asymmetry factor

$$\frac{|p_{13}n_{23}\text{Amp}_{\text{healthy}}| - |p_{13}n_{23}\text{Amp}_{\text{lesion}}|}{|p_{13}n_{23}\text{Amp}_{\text{healthy}}| + |p_{13}n_{23}\text{Amp}_{\text{lesion}}|} \times 100$$

of the normalized p13-n23 amplitude was <30%. The results for the normal group concur with those reported previously by Welgampola and Colebatch [11].

### SVV testing

Utricle function was tested by estimation of the subjective visual vertical during UC. A dual-axis human rotator (Neurokinetics Inc.) with lateral chair translation was employed for eccentric displacement

profiles. This enabled testing in the three positions: with the head centric on-axis, left ear eccentric, right ear eccentric. Details of this equipment and stimulus technique have been published previously [5,10].

A luminous line 20 cm in length, mounted at the centre of a black dome with a diameter of 60 cm was employed as stimulus. The dome was fixed approximately 40 cm in front of the seated subject with its centre in line with the test subject's naso-occipital axis. This permitted free field-of-view, binocular viewing of the stimulus. The head was fixed by a helmet with inflatable cushions. Estimation and measurement of the SVV were performed in otherwise total darkness. The SVV is defined here as the set angle, as measured with reference to the true vertical. The test subjects/patients were instructed to rotate the motor-driven luminous line by pushbutton, such that the line was aligned to the gravitational vertical, and then to confirm the setting. Between trials, the line was switched off and rotated to a random position under program control, and the procedure was repeated. SVV estimation was performed in this manner three to five times. The resulting median values were employed in the subsequent evaluation.

The UC stimulus profile consists of a spin-up with angular acceleration ( $3^\circ/\text{s}^2$ ) around the earth-vertical z-axis up to an angular rate of  $300^\circ/\text{s}$ . SVV estimation was commenced after at least 2 min of constant angular rate rotation to ensure extinction of any per rotatory nystagmus and its possible influence on the SVV setting. Unilateral stimulation was generated by translating the subject chair radially by  $\pm 3.5$  cm from the vertical rotation axis during constant velocity rotation at a rate of 1 cm/s. Thus, the eccentric labyrinth is exposed to a force equivalent to  $\omega r^2$  along the interaural axis, while the opposite labyrinth is positioned on-axis and therefore exposed to zero centrifugal force. This corresponds to an effective tilt of the gravito-inertial vector at the centrifuged labyrinth of  $11^\circ$ .

A consistent order of testing in the three positions was maintained. Testing during rotation was commenced with the patient in the on-centre position. Then the patient was translated so that the presumed healthy ear was eccentric and testing continued in this position. Next, the presumed lesioned ear was positioned eccentrically for testing. Thereafter the patient was returned to the on-centre position and final trials were performed before the chair was decelerated. This procedure is equivalent to that used, for example, for pure-tone audiometry. In those cases where the lesioned side was not indicated, a random order was performed. On average, a period of 3–5 min was required for testing in each position. The entire procedure lasted approximately 20 min.

The SVV test was classified as pathological when the median across the trials performed with the lesioned ear lay beyond the normal range (see example in Figure 1). The normal response range is based on tests performed with 43 healthy subjects (15 female, 28 male, aged between 15 and 52 years, median 27 years) who had been screened for any symptoms of vestibular or neurologic diseases, and who were required to be alert and to have abstained from consumption of alcohol or any medication during the preceding 24 h.

The 5–95% distribution of the SVV estimates of the control group were determined as: on-centre ( $-1.99 < 1.99$ ), right eccentric ( $-10.19 < -3.16$ ) and left eccentric ( $10.19 < 3.16$ ). The normal range is also included in the patients vs controls comparisons shown in Figures 1 and 2.

The SVV asymmetry factor was calculated from the median values of the set of trials performed with the healthy ear, and with the lesioned ear, while subjected to UC:

$$\text{SVV asymmetry} = \frac{|\text{SVV}_{\text{healthy}}| - |\text{SVV}_{\text{lesion}}|}{|\text{SVV}_{\text{healthy}}| + |\text{SVV}_{\text{lesion}}|} \times 100$$

Based on the 5–95% distribution of SVV asymmetry values from the control group the normal threshold was defined as 35%.

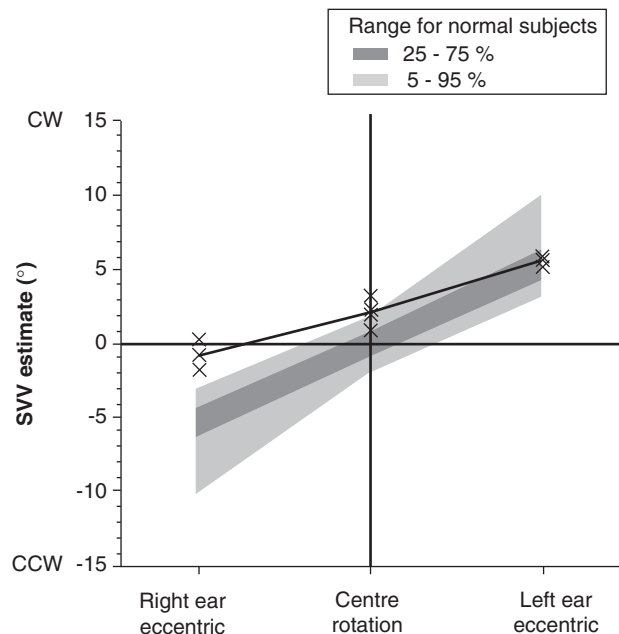


Figure 1. Example of SVV test results in a patient with dysfunction of the right utricle. The SVV estimates of each individual in each of the three tested positions (UC right, UC left and on-centre rotation) are shown as crosses. The 25–75% and 5–95% ranges for normal subjects are indicated by the dark and light grey areas, respectively. Note also that the patient's estimates while rotated on-centre also indicated a tilt perception towards the healthy ear (see Discussion for details).

Table I. Classification and incidence of presumed diagnoses and reported symptoms.

Presumed diagnoses	Incidence	
	Vertigo	Dizziness
Spontaneous onset		
Otolith dysfunction	...	15 (25)
Loss of vestibular function	15 (47)	... (5)
Post-traumatic onset		
Post-traumatic vertigo	2 (8)	11 (13)
BPPV	2 (3)	1 (1)
Gentamicin effects	... (4)	... (4)

The presumed diagnoses are based solely on the case history and symptoms reported during the initial examination. Numbers are listed for the 46 patients with isolated unilateral utricle dysfunction; those in brackets specify incidence among the 110 patients included in the study.

### Statistical testing

The distributions of the test results are presented as box-and-whiskers plots (minimum and maximum, 5–95% percentiles, 25–75% quartiles, median, mean as small square). Statistical testing of healthy versus lesioned ear measurements was performed with the Wilcoxon test for dependent samples (paired differences). Statistical testing of patient versus normal data was performed with the U-Mann-Whitney and Kruskal-Wallis tests. A significance level of  $p < 0.05$  was employed.

The experimental protocols employed were approved by the Ethics Committee of the Charité Medical School and concur with the Helsinki Declaration.

### Results

Forty-six patients (23 female, 23 male) fulfilled the criteria for inclusion in the study. This group of patients were aged between 18 and 77 years (median 51.5 years). In 24 cases the disorder was identified in the right ear and in 22 in the left ear. The median interval between initial occurrence of symptoms and examination was 17 months. Of the 46 cases, 27 presented with complaints of general dizziness and postural instability while 19 reported rotatory vertigo. In 30 cases the complaint had occurred spontaneously; in 16 cases the complaints had resulted from trauma. These data are summarized in Table I.

The 64 patients who did not fulfil the selection criteria displayed a variety of findings. Eleven showed normal responses while 12 had asymmetric responses

in all 3 tests. A further 11 showed symmetric caloric responses but asymmetric responses in the VEMP and SVV tests. Four patients consistently underestimated and 13 overestimated the vertical during stimulation of either labyrinth. The remaining 13 were found to have various other combinations in their test results.

### Caloric testing

The distribution of the SPV values (sum of absolute response intensities for 44°C and 30°C irrigations) yields a median response from the healthy ear of 48.2°/s, and from the lesioned ear 48.5°/s, indicating normal symmetric function of the lateral SCCs. Statistical testing (Wilcoxon, paired differences) verified that no difference existed ( $p = 0.46$ ).

### Vestibular evoked myogenic potentials

The distributions of the normalized VEMP amplitudes (p13–n23) for the healthy and lesioned ears of the 46 patients demonstrate the symmetry of the responses (medians: healthy, 0.70; lesioned, 0.66). As for caloric testing no significant difference was found between healthy and lesioned ears (Wilcoxon, paired differences,  $p = 0.35$ ).

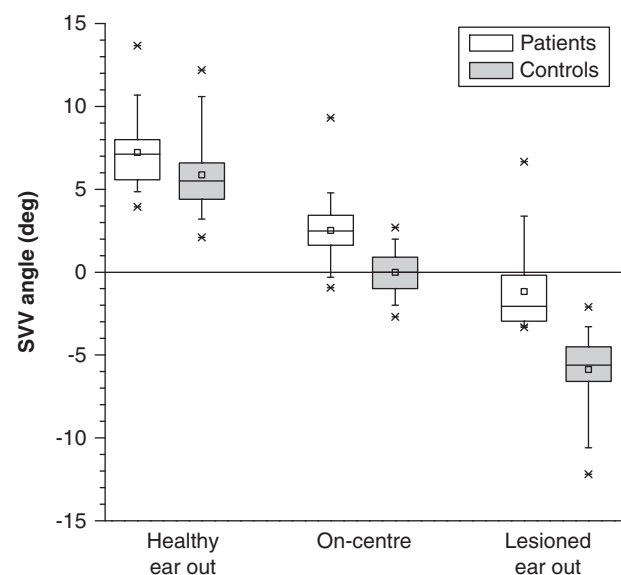


Figure 2. Distributions of SVV estimates ( $n = 46$  patients) during unilateral stimulation of the healthy and lesioned ears, and during on-centre rotation. The distributions for the normal collective are shown for comparison (shaded grey). The patients' responses differ significantly from those of the controls, both when the lesioned ear is centrifuged and during on-centre rotation (see Discussion).

### Subjective visual vertical

The results of SVV estimation during UC are summarized in Figure 2. The median SVV estimate for the healthy ear was  $7.2^\circ$  (min/max =  $3.9^\circ/13.7^\circ$ ). The SVV estimates obtained during testing of the lesioned ear lie distinctly outwith the normal range and are distributed close to  $0^\circ$  (median  $-2.0^\circ$ , min/max  $-3.7^\circ/6.7^\circ$ ), indicating that little or no tilt perception was mediated from this otolith organ. During on-centre rotation the SVV estimates ranged between  $-0.9^\circ$  and  $9.3^\circ$  (median  $2.5^\circ$ ).

Statistical testing verified that the responses for the healthy and the lesioned ear differed significantly (Wilcoxon,  $p < 0.001$ ). Comparison of the responses for the lesioned ears and the on-centre results with those of a normal collective also yielded a highly significant difference (Mann-Whitney,  $p < 0.001$ ).

### Asymmetries

In the case of caloric testing, the asymmetry factors were distributed close to zero (median  $-1\%$ , min  $-23\%$ , max  $25\%$ ). The VEMP asymmetry factors were also distributed around a near-zero median (median  $5\%$ , min  $-26\%$ , max  $27\%$ ). In contrast, the asymmetry factors for SVV during UC deviated significantly from zero (median  $48\%$ , min  $22\%$ , max  $98\%$ ), reflecting the peripheral loss in the lesioned ear. Statistical testing verified that the asymmetry factors of the SVV test results in the patients differed significantly from those calculated for caloric testing and for VEMPs ( $p < 0.001$ ).

### Discussion

While the present analysis cannot be considered as an epidemiological study, evidence is presented demonstrating that from a sample ( $n = 110$ ) from the patient population presenting to the dizziness clinic, the possibility of a unilateral isolated utricular dysfunction was found in 46 cases, i.e. by exclusion of SCC dysfunction based on caloric testing, and saccular dysfunction based on VEMP testing.

The validity of this proposal is dependent on the sensitivity and specificity of these tests. While VEMP measurements are subject to various artifacts (middle ear disorders, electrode impedance, muscle activity) the measurement of unequivocal symmetric responses is generally accepted as a reliable indication of normal bilateral saccule function. The use of the caloric test for determining semicircular canal function is limited by the fact that a caloric irrigation presents a low frequency stimulus to the labyrinth. There is evidence

that the head impulse test [12] complements this as a high frequency test. While a few studies have indicated that the head impulse test with subjective observation is primarily useful in cases of severe canal paresis [13], recent reports [14,15] have demonstrated that the use of scleral coils for recording eye and head movement during head impulse testing increases the sensitivity of this test substantially. However, this measurement technique is not practicable in the clinical routine. Given these reports, the present findings of symmetric caloric responses do not exclude entirely the possibility of canal hypofunction.

In a previous study [5] we demonstrated that the SVV during UC, in addition to its high specificity, has a high sensitivity to utricle dysfunction. With regard to the possibility that the present SVV responses might be false positive or type I errors it is pointed out that, as specified by the 5–95% confidence limits defining our normal range of SVV estimates, the probability of such errors is nominally 10%. The incidence of 46 of 110 (41.8%) exceeds this threshold considerably and would exclude this possibility.

It has been reported previously that vestibular neuritis does not necessarily affect the complete labyrinth, but can involve only a partial loss of vestibular function, specifically of the lateral SCC and the utricle, which are reliant on the superior division of the vestibular nerve [16]. The results of the present study concur with this observation and indicate that even more specific lesions of the utricular nerve branch may occur and/or persist after initial recovery.

Taken together with the reported prevalence of canal hypofunction [14] in cases of chronic vestibular deficit, a pattern of combined utricle and high frequency canal hypofunction after initial recovery emerges. It is also suggested here that the maculae of the utricles may be prone to enduring damage after apparent recovery from injury to or infection of the labyrinth due to their more complex cellular structure, involving several thousand sensory and supporting cells and the associated complex of neuronal interconnections.

Influence of the vertical SCCs on the symmetry of the SVV can be ruled out for the present test protocol. Any response of the vertical SCCs, which may induce changes in torsional eye position [17] due to the angular acceleration phase of the rotation profile, would have extinguished within the 2 min interval at constant angular velocity that is maintained before commencing with the SVV trials.

The finding of normal saccule function in the 46 patients with asymmetric SVV during UC also confirms the predominant role of the afferent information from the utricles in SVV estimation. This in itself verifies the efficacy of SVV testing during UC for the examination of utricular function.

On the basis of case history and preliminary examination an otolith dysfunction was initially suspected in 15 of the 46 cases. Fifteen cases were prediagnosed as unilateral peripheral vestibular dysfunction, 13 as post-traumatic vertigo and 3 as BPPV. In all of these 46 cases, however, caloric and VEMP testing yielded symmetric right/left responses. It should be noted, as previously reported [18], that symptoms described by patients on initial examination do not necessarily correlate with the results of the subsequent functional tests, e.g. unilateral peripheral vestibular dysfunction with initial symptoms of rotatory vertigo is not always strictly associated with SCC dysfunction, but can also involve degeneration in the utricle. In the three cases of BPPV it is likely that an otolith dysfunction, as such, could persist despite successful therapy. Such association between BPPV and otolith dysfunction has already been reported [19,20].

With the present paradigms, utricular hypofunction could be identified solely by SVV testing during UC. Otherwise the aetiology of the disorders would have remained unclear. In particular, as we have previously shown [5], testing SVV with head and body tilt would, in many cases, fail to reveal the unilateral dysfunction on account of central vestibular adaptation.

The findings also support the earlier observation [18] that, for screening purposes, useful information can be obtained from testing with conventional on-centre rotation. Thus, with the subject positioned with head centre on-axis, the right and left utricles are subject to equal and opposite stimulation, which in turn enhances any right-left asymmetry in tilt perception and thus in SVV estimation (cf. Figure 2). This observation could be put to use for screening patients with SVV estimation on a conventional rotating chair.

The findings demonstrate that for clinical practice – given symmetric caloric responses (asymmetry < 25%) and symmetric VEMPs (asymmetry < 30%) – SVV estimates during UC that lie outwith the 5–95% normal range and yield an asymmetry > 35%, a unilateral utricle hypofunction is indicated.

In summary, the present findings demonstrate that an enduring unilateral utricular hypofunction can occur after disease of, or injury to the labyrinth, as appears to be the case for high frequency canal hypofunction [15]. The findings also suggest the possibility of a unilateral isolated utricular dysfunction – or utricle paresis – as a novel category of peripheral vestibular dysfunction. All told, the findings provide further refinement of the differential diagnosis of peripheral vestibular function.

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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