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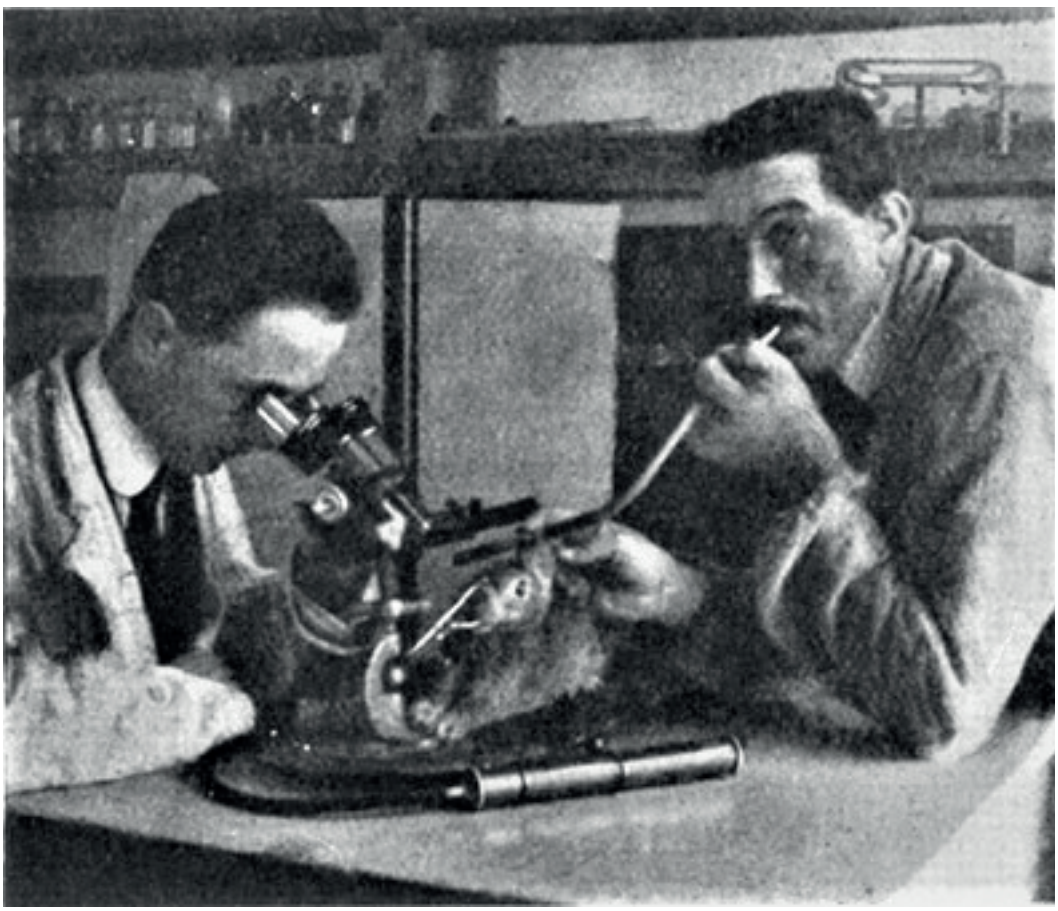
Development of Vestibular Evoked Myogenic Potentials and Audiometry for the clinical diagnosis of Superior Canal Dehiscence Syndrome



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DEVELOPMENT OF VESTIBULAR EVOKED MYOGENIC POTENTIALS AND AUDIOMETRY FOR THE CLINICAL DIAGNOSIS OF SUPERIOR CANAL DEHISCENCE SYNDROME

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Dr. Pietro Tullio and assistant during an experiment on sound induced eye movements in a rabbit.

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Development of Vestibular Evoked Myogenic Potentials and Audiometry for the clinical diagnosis of Superior Canal Dehiscence Syndrome

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To the memory of a great person, a brilliant clinician and my professional inspiration: my father.

ABSTRACT

Often in Audiology and Neurotology the focus is on disorders characterized by loss of hearing and vestibular function. A complementary approach is to look at the manifestations of abnormally augmented auditory or vestibular functions, commonly named auditory and vestibular hypersensitivity. The present thesis deals with several aspects of a prototype of hypersensitivity syndrome, the superior canal dehiscence syndrome (SCDS). This relatively rare syndrome is characterized by cochlear and vestibular hypersensitivity to sound and vibrations, but also to pressure stimulation which normally has no influence on hearing or balance. By use of a recently introduced vestibular test method, vestibular evoked myogenic potentials (VEMP), it is possible to obtain an objective measure of vestibular sensitivity to sound and vibrations. The thesis describes the background to the research field presenting: the normal function of the ear, the function in presence of conditions giving sound/vibration and pressure hypersensitivity (third mobile window syndromes), a detailed description regarding the superior canal dehiscence syndrome and the vestibular evoked myogenic potentials. The thesis then presents and discuss in details the four scientific papers which are the core of this research project.

In the first paper a new vestibular evoked myogenic method is presented. This method, based on low frequency bone conducted stimulation, showed a high diagnostic ability for SCDS, especially valuable in those sporadic conditions when other methods, based on sound stimulation, cannot be applied.

The second paper presents a new approach for testing the cochlear hypersensitivity to body sounds. This phenomenon, expressed clinically by the symptom autophony, is particularly evident in SCDS. The study showed that it is possible to retrieve a measure of the internal body sound hypersensitivity by means of a specific audiometric application based on the delivery of bone conducted stimuli at distance sites and not at the mastoid as normally performed.

The third paper is a comparative study on the actual ocular VEMP (oVEMP) methods investigating their diagnostic ability for SCDS in a large cohort of dizzy patients. The study confirmed the diagnostic superiority of oVEMP evoked by sound stimuli over the two other methods based on oVEMP evoked by bone conducted stimuli.

In the fourth paper SCDS the diagnostic ability of sound induced VEMP protocols is studied. The testing is performed at reduced stimulus intensity levels according to the newly released recommendation on acoustic stimulation restrictions during VEMP testing. Specifically, VEMP was tested at sound intensity levels compatible with safe acoustic exposure levels in audiological testing. The study showed that these reduced sound levels did not affect the diagnostic accuracy of VEMP for SCDS. This is clinically relevant, as it will make it possible to carry out a SCDS diagnosis even among patients affected by abnormal acoustic susceptibility.

LIST OF SCIENTIFIC PAPERS

I. *Ocular vestibular evoked myogenic potentials to vertex low frequency vibration as a diagnostic test for superior canal dehiscence*. Verrecchia L, Westin M, Duan M, Brantberg K. Clin Neurophysiol. 2016 Apr;127(4):2134-9. doi:10.1016/j.clinph.2016.01.001.

II. *Enhanced Auditory Sensitivity to Body Vibrations in Superior Canal Dehiscence Syndrome*. Brantberg K, Verrecchia L, Westin M. Audiol Neurootol. 2016;21(6):365-371. doi: 10.1159/000450936.

III. *Diagnostic Accuracy of Ocular Vestibular Evoked Myogenic Potentials for Superior Canal Dehiscence Syndrome in a Large Cohort of Dizzy Patients.* Verrecchia L, Brantberg K, Tawfique Z, Duan M. Ear Hear. 2018 Jun 7. doi:10.1097/AUD.0000000000000613.

IV. *Vestibular myogenic potentials evoked by air conducted stimuli at safe acoustic intensity levels retain optimal diagnostic properties for superior canal dehiscence syndrome.*Verrecchia L, Glad K, Frisk R, Duan M. Manuscript

CONTENTS

LIST OF ABBREVIATIONS

AC	Air conducted
AR	Asymmetry Ratio
AUC	Area under the curve
BC	Bone conducted
C7	Seventh cervical vertebra stimulation point
CH	Conductive Hyperacusis
CT	Computerized Tomography
cVEMP	Cervical VEMP
Cz	Midsagittal vertex stimulation point
dB	decibels
EMG	Electromyography
Fz	Midsagittal forehead stimulation point
HC	Healthy controls
ICVD	International Classification of Vestibular Disorders
ILD	Interaural latency difference
$L_{Aeq,8h}$	(dB) sound exposure equivalent level, A weighted, 8 h
nHL	(dB) normalized hearing level
N	Negative peak at VEMP
oVEMP	Ocular VEMP
peFL	(dB) peak-to-peak equivalent force level
P	Positive peak at VEMP
REL	Recommended exposure levels
ROC	Receivere Operator Characteristic (curve)
S(S)CDS	Superior (semicircular) canal dehiscence syndrome
SCM	Sternocleidomastoideus muscle
SPL	(dB) sound pressure level
STC	Soft tissue conduction
VEMP	Vestibular evoked myogenic potentials
VN	Vestibular neuritis
VOR	Vestibular ocular reflex

1 BACKGROUND

Although the ear is most often related to the hearing, it also serves another less apparent yet equally fundamental function, the *vestibular* function that represent the detection of head positions and movements. The hearing and vestibular functions are made possible by the activity of a functional unit: the hair cell. In the ear the hair cell acts as a mechanoreceptor, i.e. a cell whose homeostasis can be perturbed by mechanical stimuli. Specifically, the hair cell is sensitive to shear forces which modify the *stereocilia* bending on the top of the cells. Although there exists biochemical and structural differences, the hair cells in the hearing and vestibular epithelia ultimately share this stimulation modality. Their functional differentiation (hearing or vestibular) depends on the anatomical arrangement of the sensory epithelium in the different parts of the inner ear and on the surrounding structures that condition the bending of the stereocilia. This thesis presents clinical aspects of a condition which deeply modifies the physiological rules of the ear organ: the *superior canal dehiscence syndrome* (SCDS). In order to better understand the biophysical changes and clinical aspects of SCDS a brief description of the ear anatomy and physiology is required.

1.1 THE NORMAL EAR

Hearing can be defined as the perception of environmental vibrations conveyed by air or other means to the ear. The ear isolates, amplifies and transduces a specific range of environmental vibrations that corresponds to our hearing spectrum (20-20.000 Hz). Different parts of the ear organ contribute to different properties of the hearing function. The outer ear (the *pinna*) conveys the frontolateral vibrations into the *external auditory canal*, a bony canal that deepens into the temporal bone. This is coated by skin annexes and ends medially with a thin concave epithelial drum, upon which the conveyed external air vibrations concentrate. The *eardrum* is in continuity with a chain of three small bones suspended in an aerated cleft of the temporal bone, the *middle ear*. The middle ear is connected with the upper airways through the *Eustachian tube*. The ossicles move around their reciprocal joints in response to eardrum vibrations, transmitting and amplifying the incoming vibrations. The medial ossicle, the *stapes*, is in contact with the inner part of the ear, through a mobile interface, the *oval window*.

The *inner ear* is a complex of bony cavities enclosed in the medial portion of the temporal bone. It is structured in two liquid-filled compartments (the perilymph and endolymph spaces) separated by membranous structures in which the sensorial epithelia are endowed. Functionally, the anterior part of the inner ear is dedicated to the hearing function with the structure known as the *cochlea*; the posterior part is dedicated to the transduction of the head stato-inertial forces known as the *labyrinth* (1). The inner ear is surrounded by the *capsula otica*, a compact bony layer with only few openings to the surrounding structures. Medially, the inner ear is connected with the intracranial structures by the *vestibular aqueduct*, the *cochlear aqueduct*, the *internal auditory canal* and the labyrinthine openings along the nerves and vessels. The connection is only anatomical, because the inner ear and the intracranial

spaces in normal conditions are functionally independent. On the contrary, the middle ear and the inner ear are functionally connected by the presence of two active openings: the *oval and round windows*. These two openings function as mobile interfaces between the gaseous cleft of the middle ear and the perilymph chamber of the inner ear. Whereas the oval window is conditioned by the presence of the stapes footplate, the round window is conformed as an elastic membrane.

The two windows are fundamental for the hearing function. In fact, given the incompressibility of the inner ear fluids, the stapes oscillations during sound stimulation are transmitted into the inner ear only by the occurrence of an opposite oscillation of the round window. The two windows are anatomically connected by the two parallel perilymphatic canals (the *scala tympani* and *scala vestibuli)* which run into the cochlea and come in contact with each other at the apex of the cochlea (fig. 1). In this way, a perilymphatic fluid displacement generated by the oval window oscillations is constrained into the cochlea to reach the round window, travelling into the cochlea perilymphatic canals. The cochlea becomes, de facto, the only inner ear portion that is influenced by the sound vibrations transmitted by the stapes. The two cochlear perilymphatic canals are separated by the *scala media*, a membranous canal filled by endolymph (fig 1.A). The cochlear sensorial epithelium is distributed in the scala media lying on a supportive elastic membrane, the *basilar membrane*, which separates the scala media from the the scala tympani. The *Reissner´s membrane* represents the other membranous interface that separates the scala vestibuli from the scala media. In the scala media a collagenous structure, the *tectorial membrane*, is anchored medially but free to flow laterally in the endolymphatic room. The tectorial membrane covers the sensory epithelium of the scala media along all the two and half turns of the cochlea. It embeds the top of cells stereocilia, regulating the cilia deflection according to the grade of fluid compression across the three cochlear canals. The basilar membrane is differently compliant along its extension to the incoming vibrations: at the basal turns it is compliant for high frequency vibrations, at the apex for the low frequency vibrations, in a continuous gradient. In this way every transmitted environmental sound/noise will be spatially and timely disarranged along the cochlea epithelium according to its composition. This process is known as the tonotopical transduction of the sound, the basis of hearing discrimination. The cochlea epithelium is innervated by the dendrites of the *Golgi´s spiral ganglion*, which lies strung into the internal wall of the bony core of the cochlea, the *modiulus*. The axons of the Golgi´s bipolar neurons constitute the auditory nerve that leaves the modiulus for the internal auditory canal into the brainstem.

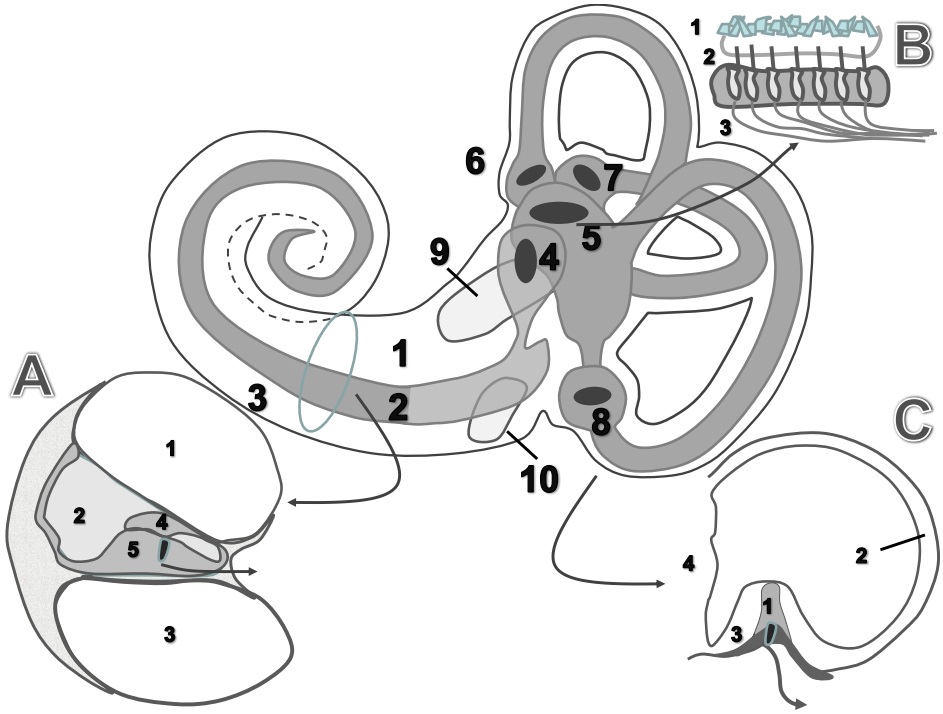


Figure 1. A schematic representation of the inner ear anatomy- medial view. In the central part the subdivision in perilymphatic spaces (transparent) and endolymphatic spaces (grey). 1. scala vestibuli; 2. scala media; 3. scala tympani. 4. sacculus; 5. utriculus; 6-7-8: ampullae of the anterior, lateral and posterior semicircular canals; 9. oval window; 10. round window. In A the section of the cochlear canal; 1.scala vestibuli; 2.scala media; 3. scala tympani; 4. tectorial membrane; 5. cochlear epithelium with evidenced an hair cell. In B a particular of the utricular macula. 1. otolith membrane with otoconia; 2. macula with evidenced the hair cells; 3. nerve endings. In C a longitudinal section of the posterior semicircular canal. 1. cupula; 2. semicircular canal; 3. sensory epithelium with evidenced an hair cell; 4.utriculus. Modified from Verrecchia et al. (2).

The labyrinth is located dorsolaterally to the cochlea and it has no functional openings towards the surrounding structures. A larger bone cavity (the *vestibulum*) is in continuity with the bony cochlea and it continues itself into three semicircular canals. Those are disposed radially, formed as semicircles and oriented on three orthogonal planes (Fig. 1). Inside those bony cavities, the membranous labyrinth, corresponding to the endolymphatic room, is functionally organized in five sensory parts. In the vestibulum there are two separate enlargements, the *sacculus* and the *utriculus*; the latter is in continuity with three membranous arms that prolong into the bony semicircular canals and end with an enlargement, the *ampulla*. The sensorial epithelium is similarly distributed in the sacculus and utriculus: it lays as a quasi-plane membrane (*macula*) that in the sacculus is oriented on sagittal plane whereas in the utriculus it is arranged on a horizontal plane. The epithelium is covered by a connective membrane (*otolith membrane*) containing a thousand of calcium carbonate crystals, called *otoconia*. Embedded in that membrane there are also the stereocilia of the underlying sensory cells (Fig 1.B). In the semicircular canals, the sensory epithelium is configured as a ridge on the medial aspect of each of the three ampullae, the *crista ampullaris*. The stereocilia of those cells are embedded in the *cupula*, a collagenous structure

conformed as a dome that covers the entire diameter of the ampulla (Fig 1.C). The cupula is anchored on the crista and free to bend on its top.

Due to its anatomical isolation, the labyrinth is only sensitive to the applied stato-inertial forces on the head. The otoconia have a higher density than the endolymph and this determines the stimulation modality of the maculae. In case of positional changes (vectorial change of the gravitational field) or in case of head movements with translational components (linear accelerations) the otolith membrane moves relatively to the macula with stereocilia deflection and cell stimulation. As an example the static gravitational field draws constantly the saccular otolith membrane downward, whereas the utricular membrane moves laterally in cases of lateral tilt. During head rotation in the plane of the macula the centrifugal force moves the otolith membrane outward.

The cupulae, in contrast, have the same density as the endolymph and they move only following an endolymph flow in the canals, a condition that is obtained by head rotation on the plane of the canal. During rotation, the inertial forces affect the endolymph column in the canals, which moves relatively to the canal walls, resulting in a lateral compression on the cupula, forced to bend in the opposite direction of head rotation. The cupula bending stimulates the hair cells by the stereocilia deflection. The tridimensional orientation of the three semicircular canals permits the detection of all the head rotations in the space by the stimulation of at least one semicircular canal.

The hair cells of the vestibular parts are in contact with the dendrites of the Scarpa Ganglion lying at the bottom of the internal auditory canal. The axons of those cells give form to the vestibular nerve, which together with the cochlear nerve, reach the brainstem and give rise to the central vestibular and auditory pathways.

Although the stimulation modalities are different (sound vibration for the cochlea and angular/linear forces for the labyrinth) the mechanism of cell activation is analogous: the stereocilia deflection by the tectorial membrane in the cochlea, and the stereocilia deflection by the cupulae or the otolith membranes in the labyrinth (1).

1.2 A THIRD MOBILE WINDOW

The presence of only two mobile windows is crucial for the normal ear function. The oval and round windows are anatomically arranged so that the sound vibrations reach and interact solely with the cochlea. The remaining inner ear is functionally isolated from the surrounding structures, making the labyrinth a head anchored stato-inertial receptor. Various conditions can alter the ear physiology by adding additional mobile interfaces between the inner ear and the surrounding structures. They are grouped under the definition of *third mobile window syndromes*. It occurs when the capsula otica is broken by one or more disruptions, which alter the functional constrains of the inner ear.

Historically, the first prototype of a third mobile window syndrome was described by Hennebert (1909) in a clinical case of otosyphilis, in which the middle ear infection eroded

the middle ear bony walls, resulting in a *perylymphatic fistula* (3). The affected patient complained of a specific symptom: the *pressure induced vertigo*. The pressure induced vertigo is the expression of a labyrinth stimulation by the middle ear pressure gradients, due to a lateral opening of the labyrinth, most often at the level of the lateral semicircular canal. Pressure changes as in swallowing, equalizing or pressuring manoeuvers in the outer ear canal can reach the labyrinth and generate a perilymph displacement with incongruous activation of the sensory epithelia. This stimulation is experienced by the subject as a transitory vertigo or a postural sway. Perilymphatic fistula may occur in cases of cholesteatoma, chronic otitis, skull base fractures and traumatic or iatrogenic temporal bone injuries (4).

Third mobile window syndromes can also develop between the inner ear and the intracranial structures. In these cases the inner ear becomes sensitive to a pressure gradient that develops between the middle ear air cleft and the intracranial spaces. An abnormal fluid displacement in the inner ear can be caused by pressuring and equalization as well as coughing, laughing, head position changes, i.e. all those conditions in which not only the middle ear but also the intracranial pressure do a transitory change. Vertigo, dizziness and balance problems occur in these circumstances, according to the same principles of incongruent vestibular stimulations mentioned for the perilymphatic fistula.

Another problem in cases of third windows syndromes is the abnormal transcranial conduction of vibrations into the inner ear. It is well known that the cochlea can be stimulated by bone conducted vibrations. Recent studies have identified five mechanisms of bone conducted hearing: (a) the air sound pressure generation in the ear canal, (b) the inertial forces on the middle ear ossicles causing a relative motion between the stapes footplate and the oval window, (c) the inertial forces acting on the cochlear fluid, (d) the alteration (compression/dilatation) of the cochlear space, and (e) the sound pressure transmission from the skull interior (5). The last one is otherwise defined as *soft tissue conduction (STC)* (6). Different lines of evidence support this modality of cochlea stimulation based on the contiguity of liquid-filled compartments and soft tissues along the whole body and more specifically between the intracranial soft tissue and the membranous structures of the inner ear. The medial openings of the capsula otica, whenever almost inert in normal conditions, could represent the possible interfaces which, in specific experimental/pathological conditions, favour a soft tissue conduction between the body and the inner ear (7). The STC can assume a major role in cochlea stimulation in case of wider or new interfaces between the inner ear and the intracranial soft tissues, such as in the cases of third mobile window syndromes.

An abnormal vibratory transmission to the inner ear manifests mainly with two clinical pictures: the *Tullio Phenomenon*, which describes a sound induced vertigo and *autophony*. The former is the manifestation of the abnormal vibratory activation of the vestibular receptors and the latter term is used to indicate an enhanced auditory perception for own body sounds. The vestibular receptors have a residual sensitivity to vibrations. Experimentally, the

sacculus is the most susceptible to vibrations, followed by the macula utriculi, the crista of the anterior, and the posterior and lateral semicircular canals (8). The Tullio phenomenon is often described as sound evoked dizziness, vertigo, postural sway, visual blur or oscillopsia. With louder stimuli, an eye movement is observed, due to the more intensive activation of the *vestibular ocular reflex* pathways (VOR) by sounds. In case of lateral semicircular canal stimulation the eyes move laterally, in case of vertical semicircular canals stimulation the eye move on a vertical torsional trajectory. The same eye movements, but induced by pressuring manoeuvers are called *Hennebert sign*. Sometimes these eye movements can assume the aspect of a transitory *nystagmus*. Tullio and Hennebert tests consist of clinical tests in which these eye movements are searched with the help of standardized loud sound stimulation or pressuring maneuvers on the outer ear.

Regarding autophony, the term can be confusing. More precisely, autophony refers to the enhanced hearing perception of own voice and it is commonly associated with another pathological condition, the *patulous Eustachian tube syndrome*. In this condition the Eustachian tube becomes an open pathway to the middle ear for the loud vibrations produced during vocal phonation. In case of third mobile window syndromes the vibrations directly reach the inner ear with enhanced perception not only of the voice, but also of the heart beating, steps, eye movements, joint movements. One can generalize and say that all body vibrations can be transmitted into the inner ear by the new opening. In this sense, autophony is a quite reductive term but nowadays largely used to indicate the cochlear hypersensitivity for internally generated sounds.

A more or less complete clinical picture of an "inward" third mobile window syndrome can be retrieved in inner ear malformations. The most representative of these being the *large vestibular aqueduct syndrome* (9), an inner ear malformation dominated by an enlargement of the vestibular aqueduct. All various grades of inner ear malformations (from the incomplete cochlear partition to the common cavity) may alter the inner ear anatomy in the sense of third mobile window syndromes (1).

Under the last three decades a new condition, SCDS, has emerged as the major exponent of the third mobile window syndromes. Nowadays, this syndrome is the first disease to suspect in case of autophony and sound or pressure induced dizziness. This thesis will focus on the diagnostic advancements in SCDS, thus this clinical condition will be presented in details in the following section.

1.3 THE SUPERIOR CANAL DEHISCENCE SYNDROME (SCDS)

In 1998 Lloyd Minor et al. (10) reported for the first time a series of 8 patients complaining about vertigo, oscillopsia and disequilibrium induced by sounds or pressure changes. All patients showed a dehiscence of the superior semicircular canal at the computerized tomography (CT) of temporal bone. Seven of these eight patients also showed vertical torsional eye movements during Tullio or Hennerbert tests. The analysis of eye movements induced by sound/pressure changes reinforced the hypothesis that these manifestations were

secondary to an abnormal sound and pressure activation of the superior canal affected by the dehiscence. In addition, the surgical correction of the bony dehiscence in two of those patients relieved the vestibular complaints. The new entity was defined by Minor as *superior semicircular canal dehiscence syndrome* (SSCDS) (11), afterwards more commonly defined as *superior canal dehiscence syndrome* (SCDS).

In the same period, Colebatch introduced a new clinical test for the study of vestibular function, the *vestibular evoked myogenic potentials* (VEMP) (12). VEMP was presented as an electrophysiological test for the study of the vestibular function, with vestibular responses evoked by loud sounds and recorded as myogenic potentials at cervical muscles. This method raised great interest, not only because it represented a valid alternative for the study of the unilateral otolith function, but more specifically for the fundamental role in the diagnosis of the newly discovered SCDS. Given the large impact in the present thesis, VEMP will be dealt with in detail in the section 1.4.

After Minor´s first report, SCDS was gradually recognized and reported on at a larger scale by various authors. Few years later Brantberg et al. (13) presented a first series of 3 SCDS patients with a specific pattern of VEMP evoked by sound stimulation (AC, air conducted). AC VEMP in SCDS were larger and reproducible at lower thresholds than in normals. This observation was replicated by other authors (14, 15). A similar VEMP pattern was not observed in other otoneurological disorders. Thus an enhanced AC VEMP response soon became a clinical marker of SCDS.

Other SCDS features were later described (16, 17): SCDS patients generally complained of autophony (hypersensitivity for body sounds); they often lateralized a midsagittal bone conducted vibration by tuning fork (Weber test) on the affected side. More specifically they could still hear on the affected side the fork moved to the ankle (18). Affected ears could show an apparent conductive hearing loss at tone audiometry, demonstrating an air bone gap more pronounced at the middle low frequencies with normal immittance tests and stapedial reflexes (19). AC thresholds were moderately affected whereas BC (bone conducted) thresholds were abnormally enhanced reaching negative values. Moreover the clinical presentation of SCDS could consist of only hearing complaints (20), mimicking, in those cases, conductive disorders with an intact ear drum, in particular otosclerosis (18). A pattern of enhanced VEMP together with normal responses at immittance tests and stapedial reflexes is highly indicative for SCDS and other third mobile window syndromes. The abnormal low BC thresholds and the positive Weber test at the extremities were considered manifestations of cochlear hypersensitivity to BC stimuli, defined as *conductive hyperacusis(CH)* (14).

Chronic dizziness, intolerance for head movements and motion induced oscillopsia (21) have been related to superior canal dysfunction in SCDS patients. However, the affected ear showed neither vestibular failure, nor hypofunction of the dehiscent superior canal (22). Pulse (23) or heartbeat synchronous eye oscillations/nystagmus (24) and also drop attacks (25) have occasionally been reported in SCDS as expressions of inappropriate vestibular stimulations by sound/pressure.

SCDS has been defined a "great otological mimicker" (26) because of the wide heterogeneity in clinical presentation. In the less severe cases, the absence of cardinal complaints, Tullio or Hennebert phenomena, makes the clinical recognition more challenging. The clinical manifestations are variably reported, however the Tullio phenomenon, (reported by the 31% - 90% of the patients according to different authors) and the autophony (60-100%) (27) are the most consistent at clinical presentation.

The prevalence in the general population has not yet been defined, but SCDS must be considered an uncommon disease. In a tertiary neurotological facility the prevalence was estimated to approximately 0.5% (27). In morphological studies (fresh temporal bone specimens (28), cadaveric studies and dry temporal specimens (29)) the prevalence of superior canal dehiscence has been estimated to 0.6% and an extremely bony thinning to 1.5%. The evidence of a dehiscence *in vivo* can be obtained by a radiological study, preferentially a high resolution CT of the temporal bone. This technique tends to overestimate the presence and dimension of semicircular canal dehiscence (30) (31). The prevalence of SCDS in CT scans *in vivo* resulted in significantly higher values that the real prevalence of bony dehiscence in dry temporal bone specimens, the former at 3.6%, the latter at 0.6% (32). The positive predictive value of CT scans has been estimated to be as low as 57% (33), whereas the negative predictive value was estimated to 91% with conventional CT reconstruction and to 97% with dedicated reconstructions (34). Larger dehiscences at CT correspond to worse hearing, larger air bone gap, lower VEMP thresholds and more disabling hearing complaints (35). A dehiscence larger than 2.5 mm has been estimated to give a complete audiovestibular SCDS picture (36).

The etiopathogenesis is still unclear. It is a common opinion that the presence of a canal dehiscence is a necessary but not a sufficient element for the development of a SCDS. A theory of "two hits" has been proposed to justify the clinical debut at middle age (10). A first causative factor is thought to be a temporal bone thickening disorder, more probably a combination of a defective development in younger age and/or an age-related osteopenia in the middle age. Indeed, the radiological prevalence of bone defects at the level of the superior canal is high in children (37), decreases in young age (38) and worsens in middle age (39).The second "hit" is often an incidental factor, such as a minor skull trauma or a wrong pressuring maneuver that can precipitate a silent canal dehiscence/thinning into a symptomatic entity. The debut of the SCDS in concomitance with minor head traumas or other incidental factors is reported in approximately half of the patients affected by SCDS (40). A "second hit" for SCDS can be for example the delivery labour (41) or a head trauma with temporal bone fracture (42).

The pathophysiology of the SCDS manifestations is an abnormal activation of the dehiscent canal by pressure, sound and vibratory stimuli. Several lines of evidence support this theory. *In vivo* the eye movement analysis showed how during a Tullio phenomenon the eye movements in SCDS were aligned with the superior canal affected by the dehiscence (43). In some patients the superior canal activation was obtained by BC vibrations (44). The enhanced

sound sensitivity in the SCDS has been reproduced by canal fenestration experiments; as well as by the canal pressure sensitivity (45).

The effect of the dehiscence on the cochlear function has been widely studied at an experimental level and also elaborated in a mathematical model (46). The presence of this additional interface at the level of the superior canal enhances the differential impedance between the scala tympani and scala vestibuli favoring the bone conduction transmission. This is thought to be the basis for the abnormally low bone-conducted thresholds and generally the conductive hyperacusis (CH). At the same time the superior canal dehiscence shunts sound induced stapes vibrations away from the cochlea resulting in decreased auditory sensitivity for air conducted sounds (47).

The diagnosis of SCDS is formulated by highly specific clinical proxies and by the visualization of a bony dehiscence at CT scanning of the temporal bone. Tullio or Hennebert signs are the most indicative manifestations of SCDS. The SCDS diagnostic criteria adopted at the Karolinska University Hospital are listed in *Table 1*.

Key symptoms	a) Vestibular hypersensitivity to loud sounds or vibrations
	b) Autophony and hearing hypersensitivity to internal sounds or vibrations
Key findings	1. Eye movements or nystagmus aligned with the affected superior semicircular canal evoked by loud sound (Tullio sign) or pressuring (Hennebert sign)
	2. Enhanced VEMP response to sound
	3. Air bone gap at 250-500 Hz ≥ 25 dB HL with normal middle ear function
	4. 256 Hz tuning fork at the ankle distinctly heard in one ear
	5. Temporal bone CT scans, reformatted on the plane of the superior semicircular canal, indicating dehiscence of the superior semicircular bony canal.
In presence of a suggestive anamnesis (a and/or b), the clinical diagnosis of SCDS is confirmed when two or more of key findings, including at least the number 5, are fulfilled. In presence of the key findings 1 and/or 2 the SCDS diagnosis can be considered with certainty, otherwise probable.	

Table 1. SCDS diagnostic criteria (Karolinska)

Analogous criteria have also been proposed (48) but still an international consensus is not available.

It is estimated that 10% of symptomatic cases do not manifest the cardinal vestibular signs of SCDS (40). This aspect together with the relatively low predictive value of the CT scan have raised more attention to the VEMP for the clinical diagnosis of SCDS. According to various studies, the diagnostic accuracy of VEMP for SCDS is exceptionally high (see 1.4). Actually, VEMP patterns of enhanced response to sound and vibrations are commonly interpreted as clinical markers of SCDS.

The surgical correction proposed by Minor et al. in 1998 (10) was indicated for the incapacitating forms. Most of the patients with minor complaints manage the SCDS conservatively. The surgical technique originally proposed was a canal plugging via a middle fossa approach. Afterwards a "capping" technique, with which the dehiscent canal is not plugged but only resurfaced, was proposed. In an unicenter review of 60 SCDS cases by Minor et al. (40), the surgery indication was necessary in 20/60 SCDS patients, with complete symptom resolution in 75% of them. According to the author, the plugging achieved long-term control more often than resurfacing. Later publications on surgical results have shown how plugging significantly improves both dizziness and autophony (49, 50) at the cost of a slight worsening of hearing at middle frequency (51) and the abolition of the canal function (22, 52). A transitory vestibular loss has been observed after surgery, especially in cases of larger dehiscences (50). Prolonged post-operative recovery due to balance complaints is more common in the presence of migraine, in dehiscences larger than 3 mm and in bilateral forms (53). The capping technique can spare the canal function but it seems not to add any advantage regarding the hearing function or auditory complaints (54). The operation of the second ear in bilateral forms can add further symptom relief (55). Considering the wide spectrum of SCDS severity, less invasive approaches than the middle fossa have also been investigated. A transmastoid approach for resurfacing (56) and plugging (57) is nowadays a doable alternative. This surgical approach is limited by a not direct visualization of the dehiscence and in some cases hindered by anatomical conditions such as a low hanging tegmen. A high rate of symptom control has been reported with transmastoid approaches in different series, both with plugging (58) and resurfacing (59). A meta-analysis showed no superiority in symptom control between middle fossa and transmastoid approaches (60). According to another systematic review the surgical management is generally effective toward the vestibular complaints, but less effective in hearing restoration (61). A minimal surgical approach has also been proposed, a transcanal/endaural round window occlusion, in which the closure of the round window is the basis for the restoration to a functional condition of two mobile windows (62). Another minimal surgical technique consists of an endoscopic middle fossa approach, for a moderately invasive access with direct visualization of the dehiscence (63). The surgery revision rate has been estimated to 10%, with a correction rate of 35% and with a risk of hearing worsening of 30% (64).

1.4 VESTIBULAR EVOKED MYOGENIC POTENTIALS (VEMP)

In 1994, Colebatch et al. (12) presented a technique for recording of sound evoked myogenic responses using cutaneous electrodes positioned on the *sternocleidomastoid muscles* (SCM). The authors demonstrated that this technique generated a highly reproducible muscle response to loud click stimuli. This response, a positive-negative deflection of the basal electromyography (EMG) had short latency and was present principally in recordings from the SCM ipsilateral to the sound stimulated ear. The amplitude of the potential was correlated to the level of the background muscular activity as well as to the loudness of the sound stimuli. The potential was suggested to be of vestibular origin, because it was present in deaf persons but disappeared in patients who had underwent vestibular neurectomy. The authors

named this sound induced response *Vestibular Evoked Myogenic Potentials* (VEMP). Since then, VEMP have been extensively investigated, both in clinical and experimental contexts. In addition, VEMP recorded from periocular muscles have also been proven to be of clinical interest (65). The periocular potentials are currently referred to as ocular VEMP (oVEMP) and the SCM potentials as cervical VEMP (cVEMP). The extraordinary clinical interest in VEMP is related to two key factors. Firstly, it is highly accessible, taking only a minor modification of routinely used auditory potential procedures to test for VEMP. Secondly, it represents the first robust and inexpensive test for unilateral otolith pathways.

In fact, accumulated evidence supports the idea that VEMP are related to otolith (saccular and utricular) function. The electrogenesis of sound evoked vestibular responses was studied in guinea pigs (66). In these studies, vestibular nerve recordings showed sound sensitive vestibular afferents also to be sensitive to static tilts, and consequently of otolith nature. Moreover, retrograde tracing, using extracellular biocytin, showed the sound sensitive afferents to originate in the striolar area of the saccular macula. As a result, a sacculo-collic pathway was suggested for sound induced cVEMP. This idea was later verified in studies on the vestibular central circuitry in a cat model (67) and by a focal lesion mapping study (68). There is also further clinical evidence for an inferior vestibular nerve pathway for the suggested cVEMP. Murofushi et al. (69) showed cVEMP present in patients with vestibular neuritis if the inferior vestibular nerve was spared. Moreover, Basta et al. (70) demonstrated SMC reactions in response to intraoperative selective inferior vestibular nerve stimulation. In summary, these studies suggested that intense sounds can activate the hair cells of the saccular macula and modulate the rest potential of first order neurons running in the inferior division of the vestibular nerve. These neurons connect to second order neuron in the vestibular nuclei, which in turn connect to the motoneuron nuclei of the accessorius nerve. Finally, the axons of these motoneurons run in the accessorius nerve to the sternocleidomastoideus muscle, i.e. concluding the three neuron sacculo-collic arc.

The vestibular nature of oVEMP has also been clinically ascertained. This periocular potential was shown to correspond to electrical activity in extraocular muscles (71, 72), particularly to the activity in the inferior oblique muscle and the inferior rectus muscle. According to animal studies (73) the oVEMP was associated with the utricular function. Utricular afferents travelling in the superior vestibular nerve were found to be activated by sounds, but even more so by low frequency bone conducted (BC) vibrations. The utricle is known to connect extensively to the eye muscles as part of the vestibule-ocular reflex (VOR). In contrast, the sacculus has only scarce connections to the eye muscles (74). Accordingly, it was speculated on whether BC vibration induced oVEMP could represent a test for utricular function and thus also for superior vestibular nerve function. Clinical observations did substantiate an utricular source for BC vibration induced oVEMP. A dissociation between AC cVEMP and BC oVEMP in patients with vestibular neuritis was demonstrated when the only superior vestibular nerve was involved (75). The oVEMP was also affected in supranuclear oftalmoplegia (76) in which the oculomotor pathway is involved and the vestibulo cervical pathway is spared. Finally the oVEMP showed stimulus directional

sensitivity (77) as well as a sensitivity for head tilt in the roll plane (78), i.e. features that are compatible with an utricular source of sensitivity for statoinertial stimulations.

VEMP can be evoked by various stimuli, such as galvanic currents and head impulses, but air conducted (AC) sounds and bone conducted (BC) skull vibrations are the most used stimulations in clinical praxis (79). Sound/vibration induced cVEMP have an optimal tuning in the middle frequencies range (500-1000 Hz) (80). Methodological standards for the clinical application of AC cVEMP have recently been released (81). The AC cVEMP is best recorded ispilaterally on a pre-activated SMC muscle and best evoked by high intensity impulsive sounds at specific frequency tunings (ex. short tone bursts at 500 Hz) not exceeding the intensity of 133 decibels sound pressure level (dB SPL).

In healthy subjects, these test standards will evoke a robust and highly reproducible positive EMG deflection at short latencies (82). The averaging of 128-192 collected responses is enough to optimize the signal/noise ratio (Fig.2). As a vestibular test, the parameters of interest of cVEMP are the response threshold and the response amplitude, whereas the latency is rather unaffected by the peripheral vestibular disorders. The cVEMP amplitude depends on the muscle activity level during testing. In order to reduce the response variance the VEMP amplitude is commonly scaled on the EMG levels before stimuli. For the study of the side difference or unilateral affections the amplitude asymmetry ratio is commonly used , with pathological cut off commonly set at 33-35% (83). Older subjects show a lower response rate, higher response thresholds and a linear amplitude/age negative function (84).

oVEMP is commonly intended as a test of unilateral utricular function. For oVEMP, an infra-orbital montage with recording electrodes under the lower eye lids was suggested (65). The response is read optimally under the contralateral eye and in upper gaze (85). Low frequency BC stimulation is preferred prior to AC stimulation. In order to deliver a symmetrical simultaneous stimulation, BC is often delivered at midline (86), at the forehead point (Fz) (87) or the vertex point (Cz) (88) preferred to others. With these specifications and after a response averaging on 128-192 sweeps, the oVEMP appears as a short latency negative-positive EMG deflection. oVEMP responses have been interpreted as the otolith phasic activation of inferior oblique muscle with a probable contribution from the inferior rectus (72) (Fig. 2). The amplitude, the threshold and the interaural asymmetry ratio are the most reported parameters for the study of the peripheral vestibular function, in analogy to cVEMP. It is, at present, probably not possible to accurately measure the muscular tension of the relevant muscles and thus it is not possible to correct oVEMP amplitude for background EMG.

At a clinical level VEMP is interpreted as a test of otolith function, but it is also utilized as a test of vestibular hypersensitivity to sound and vibrations, a phenomenon which characterizes the SCDS.

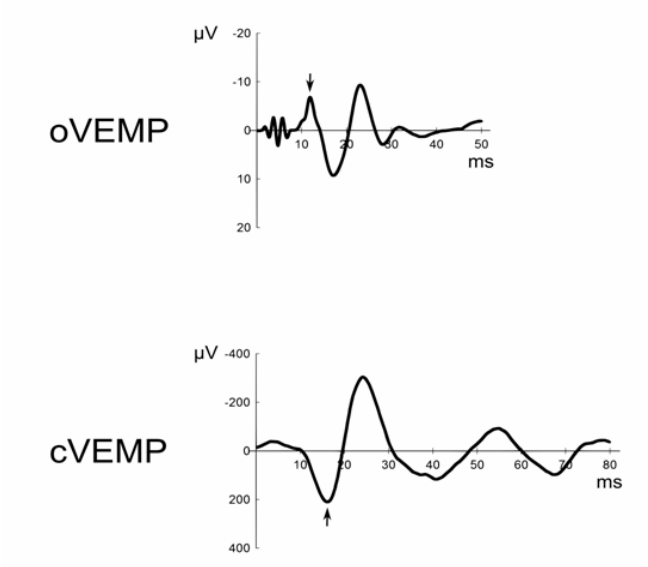


Figure 2. oVEMP and cVEMP. The typical negative-positive deflection of oVEMP and positive negative deflection of cVEMP. The first peak is indicated with an arrow. Modified from Verrecchia et al. (2).

In 1998, Colebatch et al. (89) used cVEMP to validate the vestibular hypersensitivity to sounds in a series of patients with Tullio phenomenon. These patients had large cVEMP amplitudes and low cVEMP thresholds (≤ 70 dB nHL) (89). Shortly after, the characteristic enhanced AC cVEMP pattern were confirmed in patients diagnosed with SCDS (13, 14). It was also shown that the hypersensitivity pattern normalized after surgical repair of the dehiscence (16). Since these early studies, the cVEMP hypersensitivity pattern has been reproduced on large scale (15). Further, a robust correlation between the size of the dehiscence and the VEMP amplitude has been demonstrated (35, 36).

The AC VEMP reproducibility is intact in those cases of SCDS with an air-bone gap at audiometry (19). In contrast, the AC VEMP is commonly reduced in middle ear disorders showing air-bone gap.

It has been shown that the hypersensitivity pattern in SCDS is not only specific for AC cVEMP, but also for the BC evoked cVEMP (90) and for oVEMP in response to both AC and BC (91, 92). Based on eye movement analysis, it has been argued that the oVEMP hypersensitivity pattern in SCDS is not only related to the utricle-ocular connection, but also to the superior semicircular canal-ocular connection. This may not be surprising considering that both the utricle and the superior semicircular canal innervate the eye muscles responsible for oVEMP (obliquus inferior muscle and rectus inferior muscle) (93).

It appears that the AC VEMP hypersensitivity specific for SCDS is much more evident at threshold (94) than at suprathreshold stimulation levels, due to a probable reflex saturation at higher input levels. AC cVEMP evoked by near threshold stimuli (90 dB nHL clicks) shows a high accuracy (92% sensitivity and 97% specificity) in diagnosing SCDS. The same result

cannot be obtained using the common suprathreshold AC stimulation levels (95). Furthermore, it seems that the normal frequency tuning (500-1000 Hz) for AC cVEMP and AC oVEMP is altered in SCDS with a widening up to 4000 Hz (96) that normalized after plugging of the affected canal (97). AC VEMP has been thus proposed as a marker of surgical SCDS correction.

The midsagittal BC oVEMP protocols show specific idiosyncrasies in the presence of SCDS (98). SCDS showed not only a significantly enhanced amplitude on the affected side at all the stimulation points but also a specific response latency pattern: delayed responses for stimuli at forehead (Fz) and anticipated responses for stimuli at Vertex (Cz). For instance, the surgical resolution of the dehiscence with "capping" resolved that latency pattern.

In conclusion, VEMP testing effectively detect SCDS with highly specific patterns of hypersensitivity for both AC and BC stimuli at both cVEMP and oVEMP. VEMP has assumed a fundamental role in the SCDS diagnosis, considering the low predictive values of the radiodiagnostics and the low prevalence of the SCDS key features.

2 AIMS

The overall aim of this thesis is to define the diagnostic value of clinical testing in SCDS. The clinical role of VEMP was already known in SCDS at the beginning of this research project. With studies I, III and IV this thesis contributes to establish the diagnostic role of VEMP in SCDS and the diagnostic accuracy of various VEMP protocols.

Moreover, study II explores the possibility to develop a test for cochlear hypersensitivity to internal sounds and vibrations and consequently a possible measure of the autophony in SCDS. The test is performed by an application of pure tone audiometry with a "distant" BC stimulation protocol.

1. Study I focused on the SCDS diagnostic accuracy of oVEMP evoked by a new stimulation protocol, based on a low frequency vibration delivered at the Cz midsagittal point. This stimulation protocol had been adopted since before at the Vestibular Laboratory, Karolinska University Hospital as the oVEMP standard testing, but its diagnostic value for SCDS was not yet defined.

2. Study II aimed to elucidate a method for quantification of autophony. The investigation tested the possibility to measure the psychoacustic threshold for body vibrations with a modified protocol for pure tone audiometry by controlled bone conducted vibrations at distant sites other than mastoid. The hypothesis was that the method could ascertain an enhanced threshold for body transmitted vibrations specifically expressed by SCDS patients.

3. Study III aimed to identify the best oVEMP diagostic protocol, among those commonly used, in order to identify SCDS patients in a cohort of patients complaining of dizziness.

4. Study IV took into account the recent recommendations about the acoustic exposure restrictions for AC VEMP testing. AC VEMP was consequently tested with stimuli reduced to acoustic safety levels in audiological testing. The utmost aim was to elucidate how this stimulus reduction influenced the diagnostic accuracy of VEMP for SCDS.

3 MATERIAL AND METHODS

3.1 SUBJECTS AND STUDY DESIGN

3.1.1 Study I

This study was designed as a case control study. 15 consecutive patients (7 females and 8 males; mean age ± SD= 41.7 ± 12.1, range: 23-63 years) with a diagnosis of unilateral SCDS were collected. The diagnosis was based on both coronal high-resolution CT scans demonstrating a dehiscence of the superior semicircular canal in symptomatic ears and a vestibular hypersensitivity to sound demonstrated at AC cVEMP evoked by 90 dB clicks, i.e. with a corrected amplitude large as or larger than 1(94).

oVEMP obtained in this SCDS group were compared to the ones retrieved in two different control groups. One consisted of 15 healthy subjects (HC) (9 females and 6 males; mean age ± SD= 41.4 ± 10.6, range: 23-63 years) and a second control group consisting of 20 patients affected by vestibular neuritis (VN) (10 females and 10 males; mean age ± SD= 48 ± 10.7, range: 18-60 years).

3.1.2 Study II

This study was designed as a case control study for the analysis of hearing acuity for internal body vibrations induced by BC stimulation at distance sites. This new test method was studied in SCDS patients and in a group of healthy subjects. 10 consecutive patients were collected (5 females and 5 males; mean age ± SD= 55.1 ± 10, range: 31-65 years) whose diagnosis was formulated on the same criteria as in study I. Some of those patients had symptoms indicating bilateral SCDS. However, only one ear was considered for each patient, the one to which a tuning fork placed at the vertex of the skull lateralized.

The control group consisted of 10 healthy subjects (7 females and 3 males; mean age ± SD= 41.6 ± 8, range: 27-54 years). For each of them an ear was randomly assigned as "test ear" for the comparative analysis.

3.1.3 Study III

This study was designed as a diagnostic accuracy study and yielded the application of three alternative oVEMP protocols for the diagnosis of SCDS among dizzy patients. The study followed the Standards for Reporting Diagnostic Accuracy Guidelines -STARD protocol (99). We evaluated an unselected consecutive cohort of patients complaining of dizziness, with a target condition of SCDS and an alternative condition represented by dizziness not associated with SCDS. SCDS was diagnosed according to the criteria listed in Table 1. The sample was collected prospectively among dizzy patients referred to vestibular testing at the Vestibular Laboratory of the Karolinska University Hospital. The sample size was calculated with a power analysis based on the results of the study I and on a α: 0.01, a power: 0.95 and

an enrolment ratio of 1/15. By these parameters, a proper sample size resulted in at least 9 SCDS subjects and 135 other dizzy patients.

150 subjects were collected, 5 discarded due to middle ear disorders. The eligible participants were 145: 10 of them had SCDS (all of them affected unilaterally) and 135 were "non-SCDS" dizzy patients. The two groups did not differ statistically in age (SCDS: 40.3 ± 12.1 years, min/max 29/62; non-SCDS: 50.4 ± 16.6, min/max 16/86, Mann-Whitney U test, $p = 0.40$) and sex (F/M ratio7/3 in SCDS and 77/58 in non-SCDS, $\chi 2$ test, $p = 0.42$). 3 subjects (1 SCDS and 2 non-SCDS) had data missing at random and so were excluded. Finally, 142 subjects were included in the study material. The group of non-SCDS subjects was further subdivided in diagnostic categories according to the diagnostic criteria for Meniere Disease, Acute unilateral Vestibulopathy, Functional Dizziness, Vestibular migraine, Bilateral vestibulopathy, Vestibular paroxysmia and Mal de Debarquement. The remaining dizzy patients not included in these diagnostic groups could be further categorized in a group consisted of unilateral vestibular affection and another group represented by dizziness associated to central or oculomotor disorders. Finally the last cases were classified as affected by dizziness with uncertain diagnosis and subdivided into the four vestibular syndromes according to international classification of vestibular disorders (ICVD) (100).

A "test ear" was defined for each patient: the one unilaterally affected in groups with specific diagnosis and the one with larger VEMP responses in the cases with uncertain diagnosis or without unilateral affection.

3.1.4 Study IV

The study IV consisted of a case control study with the main objective to determine the SCDS diagnostic properties of AC VEMP at reduced stimulus intensity levels. The sample was constituted by 10 subjects (7 females and 3 males; mean age ± SD= 53.7 ± 12.5) affected by unilateral SCDS according to the diagnostic criteria listed in Table 1 and 10 healthy subjects (7 females and 3 males; mean age ± SD= 46.2 ± 14.9). For the subjects in the control group a reference side was randomly assigned and compared with the affected side in SCDS group.

3.2 METHODS

The studies I,III and IV yielded VEMP testing in SCDS patients versus non SCDS subjects. The study I focused on the oVEMP evoked by low frequency vibration (single cycle 125 Hz tone-bursts at 135 dB re 1 µN peak-to-peak equivalent force level -peFL-, repetition rate: 5 Hz, 192 collected sweeps). Study III compared the three most common oVEMP protocols used in clinical practice: that evoked by midline BC Fz stimulation, that evoked by midline BC Cz stimulation and that evoked by AC unilateral stimulation. For the first two BC protocols the stimulus specifications were the same as for the study I. For the AC oVEMP the stimulus specifications were: 500 Hz tone burst at 125 dB SPL with configuration 1:2:1, 5 Hz rate, delivered by earphones TDH49-P. The oVEMP response was the result of the recording,

amplification, filtration and averaging of 192 sweeps for the three stimulation protocols applied in each tested subject.

In study IV the VEMP was evoked by AC stimuli (tone bursts at 80 dB nHL -103 dB SPL- with configuration 2:2:2, 5 Hz stimulation rate by TDH49-P earphones) and recorded at both oVEMP and cVEMP. The responses were the result of the collection and processing (amplification, filtration and averaging) of only 128 sweeps.

VEMP parameters considered for data analysis in study I, III, IV were:

- VEMP amplitude: the amplitude of the EMG positive negative deflection characteristic for cVEMP (study IV) and the amplitude for the negative positive deflection caractheristic for oVEMP (study I,III and IV) in μVolts. The absolute amplitude at cVEMP was converted into corrected amplitude, scaling the value on the pre-stimulus EMG level, according to the international standards (81).
- VEMP latency: intended as the latency of the first oVEMP peak (N1) in msec (study I and III). In study IV, no latency parameters were taken into consideration.
- VEMP amplitude asymmetry ratio (AR): amplitude side difference calculated on oVEMP in studies I and III. AR was calculated as the ratio of the amplitude difference between affected and non-affected sides over their sum. In the fourth study, no AR was taken into consideration.
- VEMP interaural latency difference (ILD): latency side difference calculated on oVEMP in studies I and III as the latency in msec of the first peak (N1) for the affected side minus the one for the unaffected side.

The second study focused on the testing of hearing thresholds for BC vibration at three "distant" sites in SCDS and healthy subjects. Commonly, the BC hearing test is conducted by mastoid vibration by conventional bone vibrator (Radiohead B71). In this study the vibration was instead delivered by a minishaker (Minishaker 4810, Bruel & Kjaer, Denmark) at Cz, at the spinous process of the 7th cervical vertebra (C7) and at the medial ankle malleolus. In order to avoid AC contamination during BC vibration at higher intensities, the ears were plugged with disposable foam ear tips, one inserted in the test ear and blocked with hot-smelt adhesive, the contralateral receiving a narrow band masking noise at 40 dB HL. Testing was performed in a soundproof booth. The subjects were asked to respond to vibratory stimulations as in a conventional audiometry test. For each of the three stimulation sites five frequencies in the range 125-1000 Hz were tested. The stimulus intensity levels were expressed in dB force level (FL) and the lowest sound perceived during vibratory stimulation determined the threshold of BC hearing perception. In case of absent perception up to 130 dB FL the threshold was arbitrarily stated at 135 dB FL.

3.3 STATISTICS

The statistical analysis yielded a) the differences in data distribution between the SCDS and non-SCDS groups, b) the analysis of tests diagnostic accuracy for SCDS. For the first

purpose, the data were elaborated on in study I and III with non-parametric tests, given the not normal distribution in the samples. In study I the within group side difference (difference in parameter distribution between the affected sides and non-affected sides) was tested with Wilcoxon matched pair test; the between group analysis (SCDS vs healthy vs vestibular neuritis groups) with Kruskal Wallis non-parametric test with post hoc analysis. Moreover a multivariable analysis (logistic regression) was attempted to value the possible effect of multiple oVEMP markers for the SCDS diagnosis. For study III the analysis yielded the SCDS/non SCDS between group analysis for each of the three tested oVEMP (BC Cz, BC Fz and AC), conducted with Mann-Whitney U Test. For studies II and IV the between and within group parameter distribution were modeled with linear mixed models for repetitive measures for normally distributed data, with post hoc analysis when suitable. For the study IV there were two linear mixed models, one for oVEMP (absolute amplitude in μVolts) and another for cVEMP (corrected amplitude).

The analysis of tests diagnostic accuracy for SCDS was approached with Receiver Operating Characteristic analysis (ROC). The area under the ROC curve (AUC) represented the main diagnostic accuracy indicator. Accuracy levels were considered acceptable when AUC resulted between 0.6 and 0.79; good, between 0.8 and 0.89 and an optimal between 0.9 and 1. Only for those parameters which showed an AUC over 0.8 (e. g. markers with relevant clinical accuracy level for SCDS) the cut-off values with best sensitivity/specificity were calculated. Furthermore, in order to ascertain whether a parameter combination was superior to a single parameter, a multiparametric ROC analysis was attempted in study III with both a simultaneous and a sequential approach.

4 RESULTS

4.1 STUDY I

oVEMP evoked by BC low frequency vertex vibration was significantly enhanced in affected ears than in unaffected ears in the 15 SCDS patients. The amplitude was 3 folds larger. The amplitude of oVEMP in SCDS ears was also significantly larger in comparison with the test ear in healthy subjects ($p < 0.001$) (Fig.3).

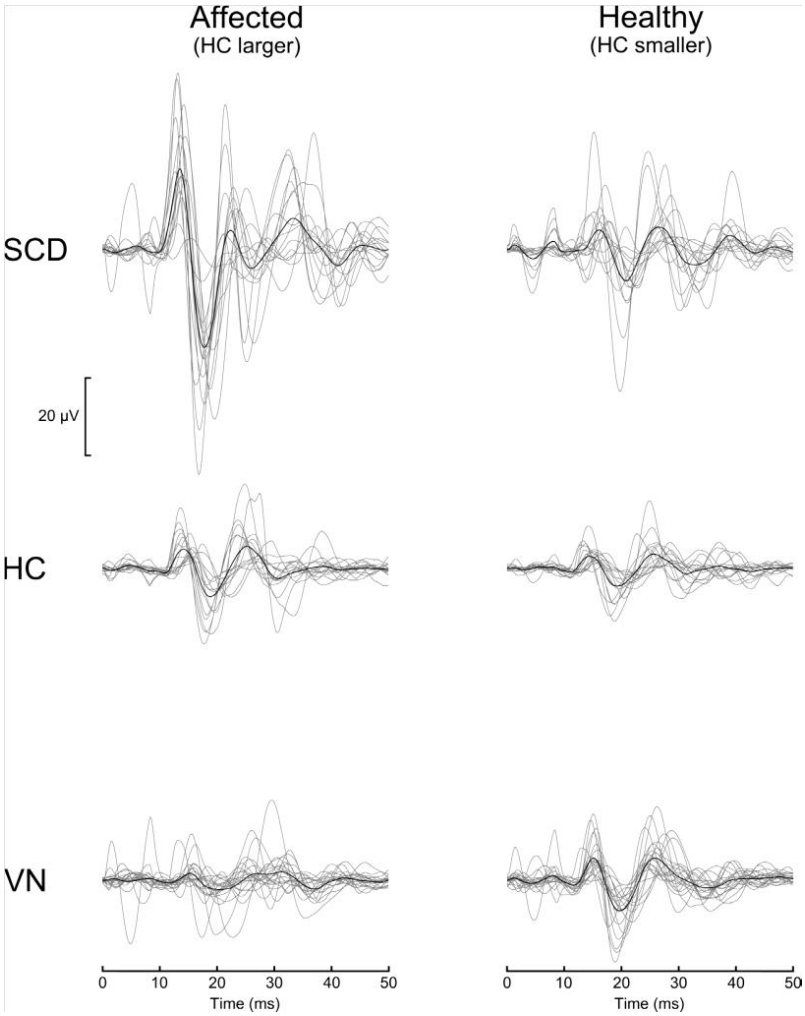


Figure 3 Graphical superimposition of oVEMP waveforms for each of the subjects in the three study groups. Left column shows traces for the affected side (SCD and VN) respectively for the side with the larger response (HC). Right column shows traces for the healthy side (SCD and VN) respectively for the side with the smaller response (HC). The bold waveforms represent the grand means

Significant differences in AR were found between SCDS and VN groups and HC and VN groups but not between SCDS and HC groups. Latency and ILD showed no statistically significant differences between the groups (Fig. 4).

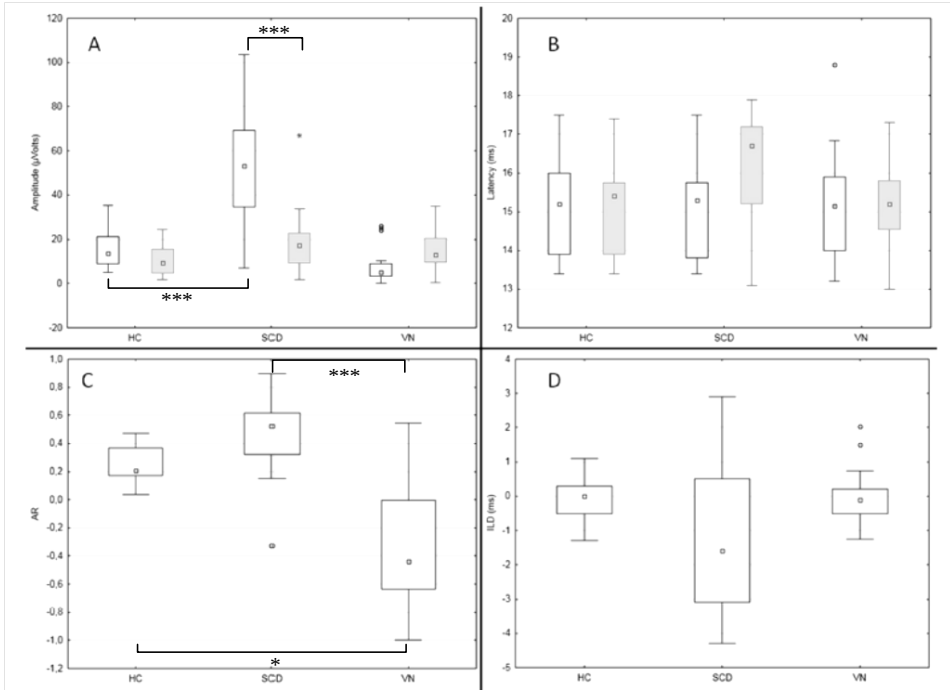


Figure 4. Parameter distribution. A) amplitude; B) latency; C) AR and D) ILD. For each panel the following three groups are indicated. Hc: healthy subjects; SCD: SCDS patients; VN: vestibular neuritis patients. The affected sides are shown as empty boxes in panels A and B. Box plots: median (point), IQR (box), distribution range (whiskers), outliers (o) and extremes (*).

The diagnostic accuracy was optimal for the amplitude parameter (AUC= 0.90) with the best cut-off value at 33.8 µVolts (sens: 87%; spec: 93%). The other three parameters had AUC < 0.8 (Fig. 5).

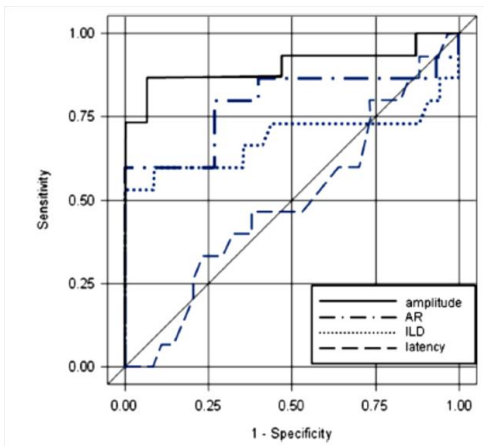


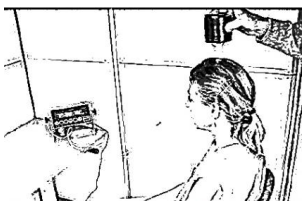
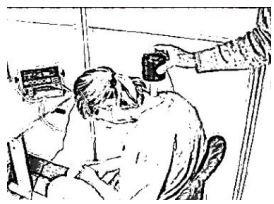
Figure 5. ROC analysis on the four oVEMP parameters.

The logistic regression analysis showed that the combination of amplitude, ILD and AR at specific cut points could return a better diagnostic accuracy (AUC=0.93) with an inverted

pattern of sensitivity/specificity: 93%/87%. When the oVEMP amplitude cut off alone (i.e. 33.8 µVolts) failed to point out the presence of a SCD the combined analysis of amplitude ILD and AR could help disclose SCD cases when the response from the affected side had en amplitude > 19.4 µVolts combined to a ILD ≤ -1.30 ms and the AR ≥ 0.21.

4.2 STUDY II

Thresholds obtained at hearing test by BC stimulation at distant points were significantly lower in SCDS than in healthy controls ($p < 0.01$). There was no significant interaction effect found between study group and stimulus site. In contrast, there was a significant ($p < 0.01$) interaction between study group and stimulus frequency, suggesting that SCD patients had enhanced auditory sensitivity for the lower frequencies. In response to vertex stimulation, frequencies up to 750 Hz differed between patients and controls. For C7 stimulation, the difference was significant up to 500 Hz. For ankle stimulation, the difference was significant for the 2 lowest tested frequencies (125 and 250 Hz) (Table 2).


	Cz, dB FL (means ±SD)					C7, dB FL (means ±SD)					Ankle, dB FL (means ±SD)				
Hz	**125**	**250**	**500**	**750**	**1000**	**125**	**250**	**500**	**750**	**1000**	**125**	**250**	**500**	**750**	**1000**
Patients	64±6	51±6	52±7	58±12	61±14	66±7	66±5	76±6	78±13	73±14	101±13	91±6	108±7	107±16	109±15
Controls	79±6	68±8	71±10	70±11	63±9	88±8	76±7	87±7	86±9	78±6	124±14	110±11	113±8	103±5	105±6
p value	<0.01	<0.01	<0.001	<0.05		<0.001	<0.001	<0.05			<0.001	<0.001			

Table 2. thresholds for Minishaker BC hearing in patients with SCDS and controls for the three stimuli (Cz, C7, Ankle)

The ROC analysis confirmed a better diagnostic accuracy for the lower stimulus frequencies: an AUC of more than 0.95 was reached for vertex stimulation in the frequency range of 125–500 Hz, for C7 stimulation in the range of 125–250 Hz, and for ankle stimulation the frequency of 250 Hz. Overall, the frequency of 250 Hz reached higher AUC levels compared with the other frequencies. The best cutoff scores for stimuli of 250 Hz differed between the 3 stimulation sites: at the vertex a stimulus of 60 dB FL separated patients with SCD syndrome from controls with a sensitivity of 100% and a specificity of 85%, at C7 a stimulus level of 67 dB FL reached a sensitivity of 89% and a specificity of 100%, and at the ankle a stimulus level of 98 dB FL reached a sensitivity of 89% and specificity of 89%.

4.3 STUDY III

Testing oVEMP with three different stimulation modalities (AC, BC Cz, BC Fz) in a cohort of dizzy patients showed specific SCDS idiosyncrasies. The amplitude was significantly larger in SCDS than in non-SCDS, regardless the stimulation modality ($p<0.001$) (Fig. 6).

Looking at the latency, the responses by BC Cz and AC were significantly anticipated in SCDS ($p<0.05$) than in non-SCDS, whereas the SCDS response was delayed in BC Fz oVEMP ($p<0.05$). The parameters referring to the side difference (AR and ILD) showed overall a major overlap between the groups. The AR was significantly larger in SCDS for BC stimulations ($p<0.05$) but not for AC oVEMP. Only in BC Fz oVEMP the responses on the affected side resulted significantly delayed in comparison to the non-affected side between the groups ($p<0.01$) (Fig. 6).

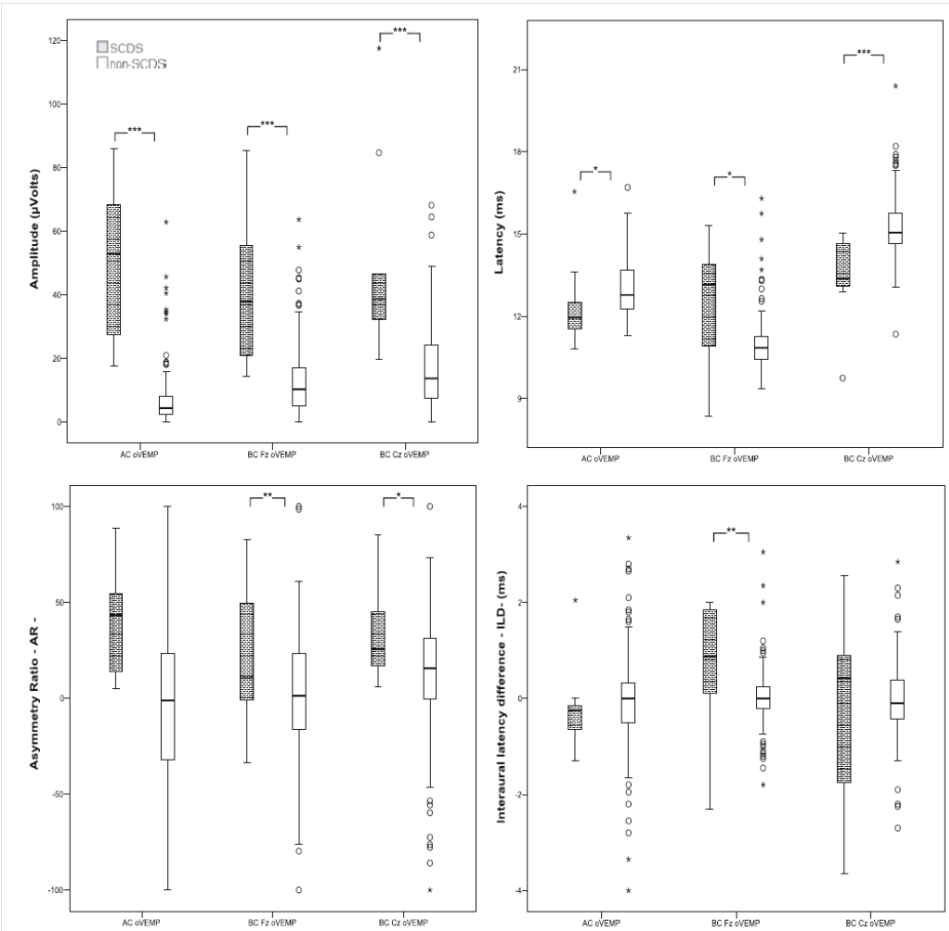


Figure 6. Distribution of the four oVEMP parameters (amplitude, latency, AR and ILD) in SCDS/non SCDS groups in response to the three different stimulation modalities (AC, BC Fz, BC Cz). Box plots indicate median, interquartile range, distribution range, outliers and extremes.Dotted boxes: cases.

According to the ROC analysis, only 4 parameters reached an AUC> 0.80, and thus valuable as SCDS markers: the AC-, BC Fz- and BC Cz oVEMP amplitude and the BC Cz oVEMP latency (Table 3).

	AUC	Best cut point	Sensitivity	Specificity
AC amplitude (μVolts)	0.965	16.7	100%	89%
BC Cz amplitude (μVolts)	0.880	31.9	80%	84%
BC Fz amplitude(μVolts)	0.890	20.7	80%	80%
BC Cz latency (ms)	0.872	14.7	90%	72%

Table 3. Diagnostic accuracy of SCDS tests based on single oVEMP parameters. Thoses with AUC > 0.8 are visualized.

Among them, the AC oVEMP amplitude was the most accurate parameter, reaching a sensitivity of 100% and specificity of 89% at a cut off of 16.7 μVolts. A ROC with a multiparametric approach limited to the four parameters from each stimulation modality, showed still a AC oVEMP superiority over BC Cz and BC Fz with an AUC level (0.96) and with amplitude, latency, AR and ILD at specific cut-offs returning a sensitivity of 88% and specificity of 96%. The optimal sensitivity of AC oVEMP amplitude for SCDS justified a ROC multiparametric analysis with sequential approach. However, the sequential adding of different parameters couldn´t improve the 89% specificity level of AC oVEMP amplitude for SCDS without reducing also markedly the test sensitivity.

Looking at the non SCDS subgroups, the AC amplitude cut off value (16.7 μVolts) could effectively separate SCDS patients from the subgroups of dizzy patients with specific diagnosis (Fig. 7). The same cut off value could also separate SCDS from the group of patients with non defined dizziness with a sensitivity of 100% and specificity of 80%.

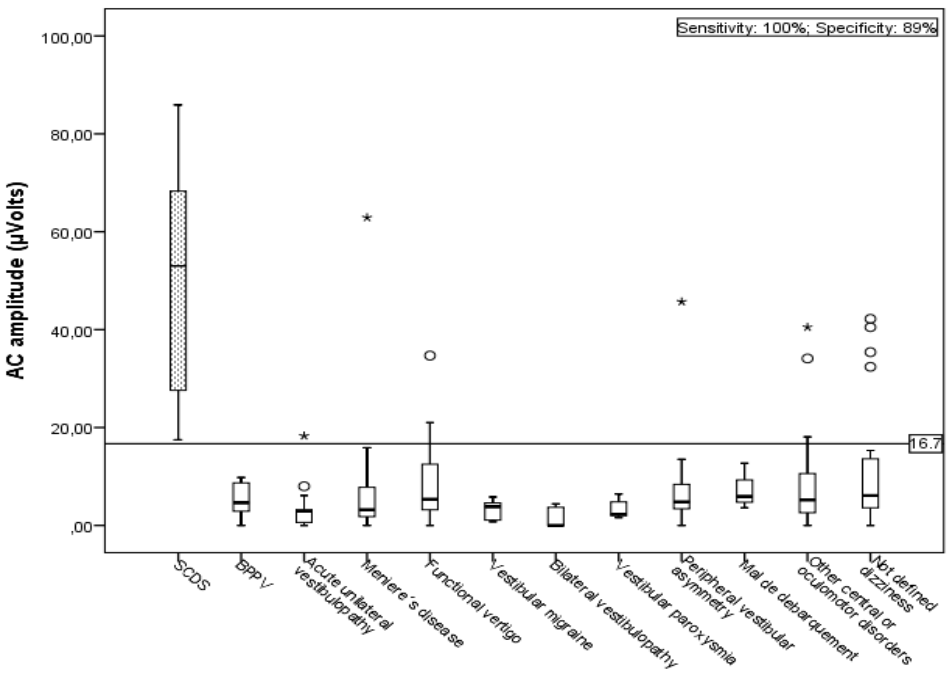


Figure 7. ACoVEMP amplitude values distribution. Comparison between SCDS group (dotted box) and diagnostic subgroups for alternative conditions. The horizontal line indicates the best amplitude cut-off in terms of sensitivity/specificity.

Values over cut offs in non-SCDS groups were found more often in BC oVEMP than in AC oVEMP with a consequent worse group separation and lower diagnostic accuracy (Fig. 8). There is no significant interaction between the subgroups and the values over cut off.

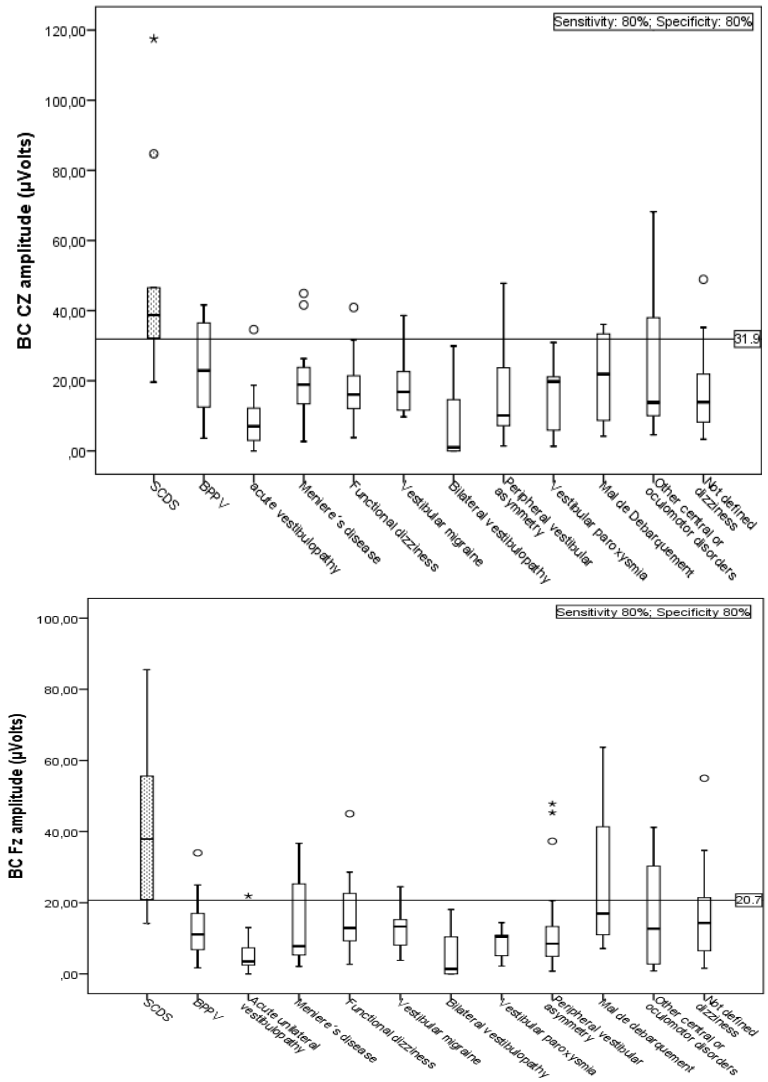


Figure 8 BC oVEMP amplitude values distribution for Cz stimulation and Fz stimulation. Comparison between SCDS group (dotted box) and diagnostic subgroups for alternative conditions. The horizontal line indicates the best amplitude cut-off in terms of sensitivity/specificity.

4.4 STUDY IV

The study stated that lowering the intensity of the AC VEMP stimuli at levels compatible with safe clinical acoustic exposure (i.e. 80 dB nHL), didn´t compromise the optimal diagnostic accuracy of VEMP. The analysis focused only on the amplitude parameter, the absolute amplitude value in oVEMP and the corrected amplitude in cVEMP. At all of the tested frequencies (500, 1000, 2000 Hz) a statistically significant separation between the

SCDS group and the healthy group was shown, at both oVEMP and cVEMP. However 500 Hz and especially at oVEMP testing, showed the best separation ability (largest group difference with lowest relative standard error) (Fig. 9).

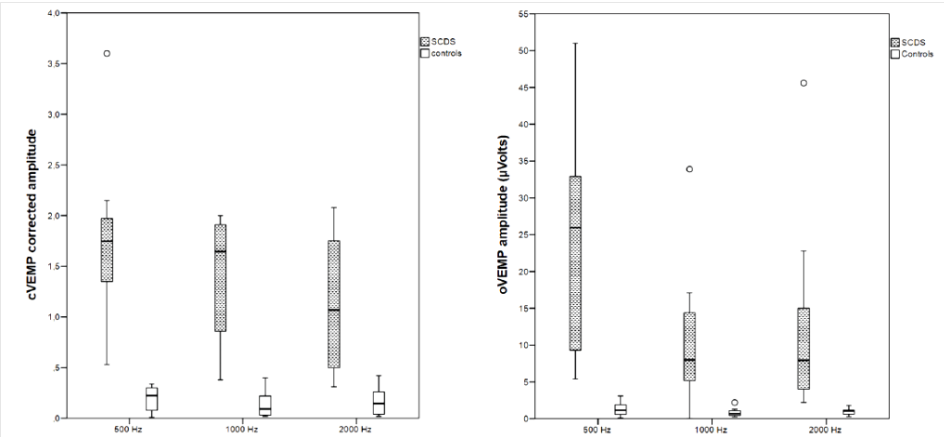


Figure 9. AC cVEMP case/control distribution in each of the three tested frequencies. Dotted boxes indicate the cases. Box plots indicate the median (line), the interquartile range (box), the distribution range (wyskers) and the outliers (o) of the parameter corrected amplitude for cVEMP (left panel) and amplitude for oVEMP (right panel).

Whereas the VEMP responses in SCDS were well reproducible and enhanced for all the subjects, this was not true for the control groups where the subjects showed a very low response rate (8%) with responses tangent to 0 value. The ROC analysis confirmed a ceiling effect when considering the AC VEMP amplitude by 500 Hz stimuli (AUC=1): this could be replicated in both oVEMP and cVEMP. Even the AC oVEMP by 2000 Hz stimuli reached a complete separation between the groups. Linear mixed model showed a weak amplitude/age correlation for cVEMP recordings but not for oVEMP. Thus, cVEMP amplitude was corrected not only for the level of EMG before stimuli but also for age. For this purpose the cVEMP amplitude was converted in corrected amplitude x age. A ROC analysis applied on this new parameter yielded a complete between group separation for both the 500 Hz and 1000 Hz recordings.

5 DISCUSSION

The clinical management of SCDS may be challenging because of the high variability in clinical presentation, with the occurrence of paucisymptomatic forms prone to misinterpretation. In fact, the key symptoms of Tullio phenomenon and autophony have been reported as low as in 60% of SCDS (27). Moreover, the highly diagnostic findings, the Tullio or Hennebert signs with eye movements aligned with the plane of the superior canal, are often hardly appreciable even in fully symptomatic patients. Noteworthy, the diagnostic accuracy of accessible supporting testing, such as audiometry, Weber test or radiological investigation, is not adequate to let them act as diagnostic proxies.

Another problem is the definition of the clinical "core" of SCDS, considering that the cochlear and vestibular hypersensitivity to sound and vibrations characteristic for SCDS, is in continuity with the variation of sound and vibration sensitivity in the healthy subjects. For this reason the SCDS diagnosis has been stated on specific criteria (Table 1), which more or less overlap with other published criteria (48). At the moment, the clinical research on SCDS is focusing on the cochlear and vestibular hypersensitivity to sound and vibrations. The main effort is to define diagnostic methods that at the same time confirm the presence of a clinically evident SCDS but also uncover a subclinical form with paucisymtomatic presentation.

The four research works discussed here are to be read in a context where the VEMP was already confirmed as a valuable diagnostic support in SCDS, in particular the AC oVEMP at suprathreshold stimulation levels (101) and for AC cVEMP at threshold levels (95). The part of the thesis that focused on VEMP aimed to improve the roll of this technique in SCDS diagnosis, by presenting new approaches (study I), by looking at the best alternative among the most common used methods (study III) and by studying the impact of the emerging sound exposure restrictions on the SCDS diagnostic ability of AC VEMP protocols (study IV).

Study II described a new method for the measure the SCDS cochlear hypersensitivity to internal sounds and its clinical correlate, the autophony. At the moment the Weber at ankle and the enhanced BC thresholds at audiometry are considered as indicator of autophony and cochlear hypersensitivity, however their SCDS diagnostic value are not completely ascertained.

5.1 STUDY I

Study I demonstrated the validity of the BC Cz oVEMP for the detection of SCDS. Previously, both AC oVEMP (101) and alternative BC oVEMP (98) showed high discrimination ability for SCDS. In previous BC Cz oVEMP studies the method was shown to be a valid and highly standardized test for the study of vestibular symmetry (88) and unilateral affection (102) and consequently it was adopted as oVEMP standard at Karolinska University Hospital Vestibular Laboratory. Confirming a diagnostic value also for SCDS by the study I, BC Cz oVEMP may function as a routine test for not only the study of utricular function and the vestibular symmetry but also for the diagnosis of SCDS.

In addition, BC Cz oVEMP has shown high levels of procedural standardisation, when compared to the other common BC oVEMP procedures, e.g. the BC Fz oVEMP (forehead) and BC oVEMP with stimulation at the mastoid. In fact, BC Cz oVEMP is conducted with the subject sitting, thus with utricular maculae in neutral position and with the Minishaker oriented with its major axis along the vertical axis, sustained only on the sides. In this way it is maintained a constant contact pressure at the vertex, given by the whole minishaker weight. In comparison, the Fz and the mastoid stimulations require that the patient is reclined backwards or lying on one side in order to align the shaker vertically (maculae not in neutral position); alternatively with patient sitting (macuale in neutral position) but with the minishaker inclined at Fz, or suspended laterally (mastoid), conditions with poorer pressure control at contact point.

The results of the study I confirm the validity of BC Cz oVEMP as a SCDS marker. The BC Cz oVEMP amplitude at specific cut point showed a good but sub-optimal test accuracy (87% sensitivity and 93% specificity). A multiparametric approach could improve the sensitivity but at a cost of the specificity reduction. Again, these values should be read in the context of the previously published results on AC oVEMP, showing a perfect diagnostic accuracy for SCDS (100% specificity/sensitivity) (101). However, in cases where the SCDS is associated to middle ear disorders (103), the AC oVEMP loses its reliability and BC oVEMP would represent the leading SCDS diagnostic test.

5.2 STUDY II

Study I, III and IV focused on VEMP as a test for the vestibular hypersensitivity to sounds and vibrations, core mechanism in SCDS. Study II focused instead on the correspondent cochlear hypersensitivity to sounds and vibrations. A measure of cochlear hypersensitivity in SCDS is important when considering that SCDS can manifest with only cochlear symptoms in up to 10% of SCDS patients (40) and that the autophony is often dominating in the clinical presentation of SCDS (60-100% of the patients) (27). Study II demonstrated a significantly enhanced cochlear sensitivity for body vibrations in SCDS patients, when compared with healthy subjects. This was true for all the three different stimulations sites at distance - Cz, the spinous process of vertebra C7 and the ankle-, however limited to the low frequency vibrations (125-250 Hz) at ankle and up to1000 Hz at more proximal sites (Cz). According to a ROC analysis, the BC stimuli at 250 Hz resulted the best in terms of group separation at all the stimulation sites. Interestingly, a 250 Hz BC stimulus at ankle at an intensity of 98 dB FL is very similar to the one produced by a 256 Hz fork at contact point. Consequently a 256 Hz fork at ankle may reveal the presence of a SCDS with a sensitivity and specificity comparable to the ones of 250 Hz minishaker vibratory stimuli at ankle (sensitivity: 89%, specificity: 89%). The SCDS enhanced cochlear sensitivity for BC vibrations at ankle could be reasonably explained by a STC mechanism. In experimental conditions it has been proven that it is possible to stimulate the cochlea by BC stimulation at distance points exclusively with soft tissue conduction, minimizing the skull bone vibration (104). Moreover the vibratory propagation for low frequency in STC seems to be independent to where the

vibration is presented. The presence of the canal dehiscence in SCDS, i.e. of a larger interface between the inner ear and the intracranial structures, may be considered the basis for the enhanced cochlear sensitivity for distant body vibrations conveyed by STC transmission.

5.3 STUDY III

To better understand which of the oVEMP procedures reported in literature had the best diagnostic value for SCDS, study III was designed as a diagnostic accuracy study for the comparison of BC Cz oVEMP, the BC Fz oVEMP and AC oVEMP on a sample of dizzy patients collected prospectively and consecutively. Among SCDS patients, 90% are supposed to suffer of dizziness or vertigo complaints, thus belonging to this cohort.

The study confirmed that among dizzy patients, AC oVEMP had a diagnostic superiority for SCDS when compared with the other two BC oVEMP modalities. The AC oVEMP amplitude was superior to the other oVEMP parameters, taken in isolation or together in multiparametric approaches. The optimal sensitivity demonstrated by AC oVEMP made this parameter a viable SCDS clinical screening tool. Moreover, the AC oVEMP amplitude separated the SCDS patients not only from the well-established dizziness diagnoses, but also from the group of dizzy patients with uncertain diagnose. This is relevant, given the possibility of a SCDS patient to manifest predominantly with unspecific vestibular complaints.

AC oVEMP tests are not reliable in patients with conductive disorders. In the sample, BC oVEMP parameters could identify SCDS; however, the diagnostic accuracy was lower. In these patients, it is advisable to use BC oVEMP parameter cut offs favoring specificity in order to minimize false positives. With the stimulus parameters used in the present study, a cut off favoring the specificity would have been 42.5 µV for Cz oVEMP amplitude (sensitivity 50%, specificity 95%), 31.7 µV for Fz oVEMP amplitude (sensitivity 70%, specificity 90%), and 13.75 ms for Fz oVEMP latency (sensitivity 50%, specificity 95%).

The generally lower diagnostic accuracy of BC oVEMP parameters may be interpreted as the result of suprathreshold saturation of BC oVEMP reflex in SCDS patients. This would reduce the tendency toward large BC oVEMP amplitude in SCDS, and consequently lessening divergence contra non-SCDS. Considering the submaximal stimulation adopted in this study to optimize the oVEMP response rate (105), BC parameters may not be optimal for differentiation of SCDS patients from others with dizziness.

Noteworthy, it appears that SCDS could have a specific latency configuration, with response anticipation when evoked by BC Cz vibrations and a response delay in case of BC Fz stimulation, compared to the test ears of the non-SCDS subjects. This pattern, reported previously (106), was confirmed in study III on a statistically significant level. A speculation on the mechanism for this latency pattern is based on the possible role of the STC. STC could imply that the vibrations may reach the cupula of the affected superior canal through the dehiscence at different timings, given the different vectorial propagation in the intracranial soft tissues of the vibration induced by BC vs Fz stimulations.

5.4 STUDY IV

Recently, spare reports (107, 108) have denounced the risk of cochlear distress during AC cVEMP. AC VEMP is commonly tested with loud AC stimuli (click, tone bursts) with amplitude often ≥125 dB SPL and with the collection of up to 192 stimulus repetitions. According to recently released expert recommendations (109), an acoustic stimulation at VEMP should not exceed the 140 dB SPL. In the case of repetitive or prolonged stimulation, it should follow the rule of a cumulative sound energy exposure given by the intensity of the stimuli and the cumulative duration of repetitive/prolonged AC stimulation. This exposure should not exceed a level equivalent to $L_{Aeq,8h}$ of 85 dB, e.g. the recommended exposure level (REL) derived by the daily safe acoustic exposure of industry workers. These recommendations represent the actual reference for safe clinical VEMP testing; however, they are based on the REL for industry workers, i.e. healthy subjects exposed to prolonged environmental acoustic stimulation. VEMP testing, on the contrary, is often conducted on patients with audiovestibular complaints in a clinical context. This cohort may express an abnormal acoustic vulnerability, especially considering patients with inner ear affection and auditory complaints such tinnitus, hyperacusis, hearing loss (110). Noteworthy is that the real acoustic vulnerability of SCDS or analogous conditions characterized by hypersensitivity to sounds and vibrations, has not been completely stated yet. In the absence of an unitary REL for acoustic stimulation in clinical testing, 80 dB nHL is suggested here to be an unquestionable safe level for audiological testing, especially for those testing with repetitive sound stimulation.

The SCDS diagnostic superiority of the previously mentioned AC oVEMP (101) has been stated for frequency specific stimuli (tone burst, 500 Hz, 6 ms, 192 repetitions) at stimulus intensity levels of 125 dB SPL. An optimal diagnostic accuracy was also observed in the cVEMP, but at the much lower intensity of 90 dB nHL click, 1 ms duration, 192 repetitions (94), with a sensitivity of 92% and a specificity of 97% for SCDS. The purpose of the study IV was to explore the diagnostic ability of AC VEMP at stimulus intensity levels compatible with safe levels of acoustic exposure in audiological testings.

AC oVEMP and AC cVEMP were tested on a small sample of SCDS patients and healthy subjects, with short stimuli (tone burst, 6 ms) at 3 different middle range frequencies (500, 1000 and 2000 Hz) and at reduced intensity levels (80 dB nHL, corresponding to 103 dB SPL), after collecting only 128 stimulus repetitions.

The study showed how this stimulus configuration didn´t invalidate the diagnostic ability of AC VEMP for SCDS. On the contrary, when the parameter amplitude was taken in consideration, the oVEMP and cVEMP could completely separate the SCDS patients from healthy subjects. This was especially true for stimuli at 500 Hz, better than1000 and 2000 Hz in group separation. Lowering the stimulus to 80 dB nHL and especially at 500 Hz tone burst stimulation, added many advantages in SCDS VEMP testing: a) the diagnostic accuracy remained optimal (100% sensitivity and 100% specificity) for oVEMP and increased to optimal levels for cVEMP; b) a SCDS screening test could be available at safe levels for

acoustic exposure in clinical testing. c) a SCDS diagnostic work up based on VEMP could be completed also in acoustic vulnerable patients minimizing the risk for cochlear distress; d) 500 Hz TB at 80 dB nHL is a stimulus protocol largely supported by the most of potential evoked devices in audiological testing. This protocol, in other words, could favour the dissemination of SCDS testing by VEMP in non experimental facilities; e) the presence of a clear response dichotomization by amplitude cut offs could ease the test conduction and the result interpretation in the clinical context. In contrast, the more diffuse diagnostic method for the SCDS is based on the search of the enhanced VEMP threshold in the affected ears, which, in comparison, presents specific drawbacks: time consuming, repetitive acoustic stimulation, difficult threshold identification in noisy recordings.

If those results could be replicated on larger samples, especially among audiovestibular patients, this AC VEMP stimulation protocol would represent the standard SCDS diagnostic VEMP protocol in the clinical context, in term of safety and feasibility.

5.5 LIMITATIONS

These four papers study the ability of different test parameters in separating SCDS patients from non-SCDS reference groups. Studies I, II and IV were designed as case control studies in which the control group was represented by healthy subjects. Most case-control studies on VEMP are sampled as SCDS patients vs healthy controls. This may add a selection bias, because there is no evidence that the healthy subjects have the same clinical behavior, in terms of test results and data distribution, as the target population where the test is really applied: dizzy patients and patients complaining of audiovestibular disorders. Study III has been consequently designed as a diagnostic accuracy study, where the target population was represented by dizzy patients accessing to laboratory testing. By this approach it became evident that the case control studies have some limitations in terms of results inference. For example the perfect SCDS diagnostic ability (100% sensitivity, 100% specificity) of AC oVEMP evidenced in a previous case control study (101) couldn´t be replicated with the same AC oVEMP protocol applied in study III. In fact, the AC oVEMP could detect SCDS patients among dizzy patients with 100% sensitivity but only 89% specificity, de facto degrading AC oVEMP from an optimal diagnostic tool to an optimal screening tool. Conversely, in a recent case-control study, with control subjects collected among dizzy patients as in study III, the author could find AC oVEMP amplitude cut offs similar to the one in study III even if they resulted in a worse group separation (111).

Another concern that could be raised in studies I, II and IV is the small sample dimension. All these samples have been however collected prospectively and were limited by the low incidence of SCDS. To be able to gather 10-15 patients affected by SCDS prospectively, it was necessary to spend two or three years of clinical activity at the diagnostic vestibular facilities of Karolinska University Hospital. This is in line with the prevalence of SCDS in a tertiary referral neurotology facility, which has been previously stated at 0,5% (27). However in the study IV, a power analysis based on the between group difference in amplitude revealed that the collected sample of 10 cases + 10 controls was large enough for results inference.

5.6 FUTURE PERSPECTIVES

- The studies discussed in this thesis define the role of clinical testing of sound and vibration hypersensitivity for the diagnosis of SCDS. VEMP and audiometry have shown a diagnostic potential in this field. More studies are needed to the find valid markers or to define the entity of sound/vibration hypersensitivity in other clinical fields, such as in the other forms of third mobile window syndromes (for example the inner ear malformations) or more in general in the field of hyperacusis.

- Diagnosing dizziness and vertigo conditions can be sometimes frustrating. Up to 18% of undiagnosis (study III) is expected among patients complaining of vertigo. The management of patients with invalidating vertigo of unclear definition is not seldom challenging. Nowadays, subjects are merged in a complex auditory environment and continuously stimulated by unnatural sounds and noise. How these factors influence the vestibular function in a context of normal or pathologic vestibular susceptibility to sound and vibrations is still unclear. More population based studies are needed to ascertain the role of sound/vibrations for the development of vestibular disorders. An unexplored field is for example the vestibular stimulation by very low or very high frequency vibrations, such the infrasounds and ultrasounds, that are not audible but that are diffuse widely in the enviroment.

6 CONCLUSIONS

Study I demonstrated the validity of low frequency BC Cz oVEMP testing for the diagnosis of SCDS. The parameter amplitude at specific cut off values could effectively separate SCDS patients from both a group of healthy controls and a group of patients affected by vestibular neuritis. Though not showing the same diagnostic accuracy of alternative VEMP protocols, BC Cz oVEMP could be a valid alternative to those methods. In particular, it could be used in those cases in which SCDS is combined with middle ear disorders, a condition in which AC VEMP loses its reliability.

Study II showed how a specific application of BC audiometry, with delivered BC stimuli at points distant from the ear, could be used to measure the cochlear hypersensitivity to internal sounds and indirectly give an objective measure of the symptom autophony. Considering that autophony is often the reason for which the SCDS patient searches for medical consultation and also the main indication for surgical SCDS correction, this BC audiometry protocol may represent not only a valid diagnostic method but also an indicator for surgical correction.

The study III confirmed that the AC oVEMP is a diagnostic test superior to the two alternative bone conducted oVEMP methods (BC Cz and BC Fz) for SCDS, specifically among dizzy patients. The parameter amplitude resulted in the best SCDS marker, with optimal sensitivity and a high specificity. Taken alone, AC oVEMP represents a low cost and feasible clinical screening method, in the context of a multistep SCDS diagnostic protocol.

Study IV showed that the already known high diagnostic accuracy of AC VEMP for SCDS, commonly evoked by loud stimulation levels, was maintained even at reduced stimulus intensities, especially at levels compatible with safe audiological testing in a clinical context. At those levels, it may be possible to perform the AC VEMP testing in those subjects particularly susceptible to acoustic stimulation, minimizing the risk of symptoms worsening or hearing loss induction. If those results could be replicated in larger series, this AC stimulation protocol may in future become the reference diagnostic test for SCDS.

7 POPULÄRVETENKAPLIG SVENSK SAMMANFATTNING

Örat har två funktioner; att vara ljudreceptor och huvudrörelsedetektor. Dessa funktioner ligger i skilda delar av örat, i snäckan (hörsel) och i labyrinten (balansen). Endast två öppningar (fönster) tillåter inkommande ljud att via hörselgång, trumhinna och hörselbenkedja ledas in i snäckan, ovala fönstret, samt att interagera med hörselcellerna, runda fönstret. Labyrinten däremot är i princip isolerad och helt bentäkt.

Vid vissa tillstånd kan örats funktion påverkas genom tillkomsten av ytterligare öppningar än de två ovannämnda. Dessa tillstånd benämns tredje fönster syndrom. Om man får ett tredje fönster som öppnar innerörat mot skallgroparna, börjar labyrinten att reagera på ljud- och tryckstimulering. Samtidigt får snäckan en ökad känslighet för interna ljud, det vill säga de som produceras i kroppen, och blir mindre mottaglig för externa ljud. Ett typiskt tredje fönstersyndrom är det så kallade takfönster syndromet (TFS), där öppningen (fönstret) ligger på högsta punkten (taket) på labyrinten. Normalt skiljer en tunn bentäckning den högsta delen av labyrinten, den främre båggången, från ovanliggande strukturer; det vill säga hjärnhinnor, cerebrospinalvätskan och hjärnvävnad i mellersta skallgropen. Öppningen agerar som ett rörligt gränssnitt och tryckförändringar i skallen eller kroppsljud når innerörat. När labyrinten felaktigt stimuleras av dessa ljud/vibrationer får man ljudframkallad yrsel (Tullios fenomen). På samma sätt när labyrinten påverkas av tryckförändringar får man tryckframkallad yrsel (Hennebert fenomen). När snäckan nås av interna ljud tillkommer autofoni, det vill säga att man hör kroppens interna ljud: puls, ögonrörelser, ledrörelser, egen röst och benledda ljud. Dessa symptom kan variera i styrka och hur de blandas och TFS kliniska presentation blir inte sällan svår att känna igen. Klinisk forskning innebär ofta att identifiera kliniska tester som kan bekräfta/avslöja tillstånd, trots dess kliniska variabilitet. Vikten av att ställa diagnos när det gäller TFS, ligger i att det kan korrigeras kirurgiskt. Särskilt de varianter som är invalidiserande.

En klinisk test med ett högt diagnostiskt värde för att påvisa TFS är VEMP (vestibulärt framkallade myogena potentialer -vestibular evoked myogenic potentials). VEMP innebär att ett muskelsvar registreras vid halsmuskler (cervical VEMP, cVEMP) eller vid ögonmuskler (ocular VEMP, oVEMP) när balansorganet stimuleras av ljud eller benvibrering. VEMP mäter i princip balansorganets känslighet för ljud och vibrationer, en funktion som är ovanligt uttalad vid TFS. Vid TFS visar VEMP ett signifikant större svar och ett svar som är utlösbart med mycket lägre stimuleringsnivåer än hos friska kontroller eller hos patienter med andra hörsel- och balansrubbningar. VEMPs svar erhålls med hög prevalens oavsett hur TFS presenterar sig kliniskt. VEMP används således idag som ett viktigt diagnostiskt verktyg för TFS.

Innevarande avhandling handlar om en utvärdering av den diagnostiska precisionen hos kliniska tester för TFS. Arbetet fokuserar huvudsakligen på VEMP, genom att undersöka och kartlägga dess förmåga att diagnostisera TFS i olika VEMP-protokoll. VEMP presenteras i två vetenskapliga publikationer och ett manus. Avhandlingen kompletteras med ett

vetenskapligt arbete om en ny mätmetod för cochleär överkänslighet för interna ljud och vibrationer, som motsvarar symptomet autofoni.

Arbete I presenterar ett nytt VEMP protokoll och dess diagnostiska precision gentemot TFS. Protokollet består av en mittlinje stimulering med lågfrekventa vibrationer (BC) på skallens hjässa (Cz) och VEMP-registrering vid ögonmusklerna (oVEMP). Studien visar att metoden med hög precision kan diagnostisera TFS när tillståndet jämförs med en grupp av friska kontroller och patienter med vestibularisneurit. I jämförelse med andra VEMP protokoll, baserade på ljudstimulering, hade BC Cz oVEMP ett mindre diagnostisk värde. Det senare protokollet kan däremot spela en större roll hos de fall där TFS blandas med mellanörestörningar, en situation där ljudframkallade VEMP inte är pålitliga.

Arbete II presenterar en särskild anpassning av hörseltest som utförs via benvibrering på ställen på avstånd från örat. Studien har sin bakgrund i den kända ökade känsligheten för kroppsljud hos patienter med TFS. Det visas att TFS patienterna är signifikant känsligare än friska försökpersoner med dessa distansvibrationer. Om dessa resultat kan upprepas på större kohorter, kan denna test vara en valid mätmetod för den autofoni som ofta är ett dominerande symptom hos TFS patienter.

Arbetet III är en jämförande studie av de vanligaste oVEMP metoderna i kliniskt bruk med syfte att utvärdera den bästa diagnostiska metoden för TFS. Arbetet designades som en diagnostisk precisions studie (diagnostic accuracy study) med ljudframkallade oVEMP och benvibreringsmetoder med stimulering vid hjässa och panna. De olika metoderna jämfördes i en kohort av yrselpatienter vari en del var diagnostiserade att hade TFS och andra hade alternativa yrseltillstånd. Studien kunde visa att ljudframkallade oVEMP var överlägsen benvibreringsmetoderna att diagnostisera TFS bland yrselpatienter. Ljudframkallad oVEMP verkade dessutom kunna vara den bästa screening testen för TFS bland yrselpatienter.

I arbete IV undersöks den diagnostiska precisionen av ljudframkallad VEMP metod när stimulering ges på mycket låga intensitets nivåer. Studien grundar sig på de nya rapporter som visar tendens till cochleär stress vid de höga ljudnivåer som rutinmässigt används vid ljudframkallad VEMP. Vid stimuleringsnivåer hos VEMP, motsvarande säkra ljudexponeringar vid hörseltester i klinisk rutin, kunde man visa att den diagnostiska förmågan för att påvisa TFS inte försämrades. Det gällde både oVEMP och cVEMP där man åstadkom en total separation av TFS patienter gentemot en grupp friska försökpersoner.

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