Vestibular Function In Vestibular Schwannoma

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Abstract

Introduction: Traditionally vestibular function has been assessed using caloric irrigations; new methods have failed to reach the same level of accuracy. Vestibular nerve dysfunction occurs with 'acoustic neuroma' or 'vestibular schwannoma. Quantitative testing of hearing by audiometry is much more widely available than quantitative vestibular testing, although consideration of vestibular dysfunction is part of clinical management. Validation of a new method of quantitative vestibular function testing could lead to more widespread integration into clinical practice and affect decision making (i.e. timing of surgery)

Methods: A non-blind observational cohort study was undertaken in 31 participants. Study endpoints were either one or two separate participant measures in March/April 2013 the September/October 13. All participants underwent caloric and head impulse testing with video-oculography, while 10 underwent audiometric assessment. Repeat testing was performed for 10 subjects, including additional cognitive. The primary outcome was vestibular function test measures.

Results: Video head impulse was strongly correlated with calorics **(p=0.01)** and showed good sensitivity (80%) and specificity (70%). Dizziness Handicap Inventory showed no correlation with other vestibular function measures. Participants showed reduced cognitive function tested using the CANTAB battery **(p=0.01)**

Conclusion: Video head impulse testing is comparable to caloric testing to assess vestibular function. Vestibular lesions may lead to cognitive deficits. Further research is needed to better understand the role of video head impulse testing in vestibular schwannoma.

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List of Abbreviations

Calorics	Bithermal Caloric Testing
cVEMP	Vestibular Evoked Myogenic Potential Cervical
dBHL	Decibel Hearing Level
EOG	Electro-oculography
FRT	Fractionated Radiotherapy
HIT	Head Impulse Test
MRI	Magnetic Resonance Imaging
NF2	Neurofibromatosis Type 2
oVEMP	Vestibular Evoked Myogenic Potential Ocular
RCT	Rotational Chair Testing
SCCs	Semi-Circular Canals
SRT	Stereotactic Radiotherapy
vHIT	Video-Oculography recorded head impulse testing
VOG	Video-Oculography
VOR	Vestibular Ocular Reflex
VS	Vestibular Schwannoma

1. Introduction

This thesis seeks to validate the use of video-oculography recorded head impulse testing (vHIT) in comparison to the traditional clinical gold standard of bithermal caloric testing (calorics) in quantifying vestibular ocular reflex (VOR) function in patients with vestibular schwannoma (VS) participants with unilateral vestibular schwannoma. Vestibular schwannoma frequently present with hearing loss and tinnitus and will impair vestibular ocular reflex (VOR) function. VideoHIT is quicker to perform and therefore more convenient than traditional methods such as calorics. This makes it an attractive alternative for measuring VOR function, potentially leading to better identification of vestibular dysfunction and improved vestibular management. The potential clinical utility of a quantitative measure of the VOR in VS is to characterize vestibular hypofunction, so aiding clinical management. For example, deteriorating vestibular function with a modest increase in VS size may indicate the need for intervention.

A secondary aim of this thesis is to investigate the relationship between vestibular lesions and cognitive function. Vestibular dysfunction has been in several cases demonstrated to produce spatial memory and cognitive function defects in both human and animal models. This thesis aims to further elucidate this connection and relate the findings to traditional vestibular function measures.

1.1 Hypothesis

My hypothesis is that video head impulse testing, as a high velocity measure of the VOR, will prove useful for detecting significant vestibular impairment among those with both symptomatic and asymptomatic VS. If validated this test would allow for documentation of vestibular dysfunction over time and potentially influence clinical management, e.g. timing of surgery, and the need for vestibular

rehabilitation following surgery.

1.2 Vestibular Impact

With lifetime prevalence of between 20%-30% dizziness is exceedingly common(4). studies from Finland and the United Kingdom estimate prevalence to be between 21-29%(5-7). Even after applying strict diagnostic criteria for vertigo, the lifetime prevalence is estimated to be 7.8%(8); though the variability of study designs makes comparisons difficult. Nonetheless, dizziness is a common problem, which can be a major health burden on populations due to its debilitating effects(9, 10), with Neuhauser(8)reporting severe impairment in up to 80% of sufferers.

Vestibular dysfunction increases the likelihood of falls, which are an established cause of morbidity and mortality in the elderly(11-14). Furthermore, the likelihood of vestibular dysfunction increases in diabetes mellitus(4). An increasing prevalence of diabetes mellitus may lead to an increased burden of morbidity and mortality from falls partially attributable to an underlying vestibular component (10, 15-17).

It is important to note vestibular dysfunction refers to any pathology affecting the vestibular system; this may or may not be symptomatic. Dizziness refers to any fault in spatial perception and stability; it is not specific and may arise from a number of systems. Vertigo is a subset of dizziness in which the individual experiences the sensation of rotation; this is frequently of vestibular origin.

It has been reported that between in 30-50% of traditional vestibular function testing methods fail to establish a localizing diagnosis(18), with multiple visits to the doctor frequently required before an appropriate diagnosis is made(4). This highlights the need for new vestibular testing methods that are easier to perform.

1.3 Vestibular Schwannoma

Vestibular schwannoma account for approximately 80% of cerebellopontine angle tumors (19-21). Vestibular schwannoma most frequently arises from the schwann cell layer of the vestibular portion of the eighth cranial nerve. As VS grow nerve compression causes auditory dysfunction, with less pronounced vestibular symptoms(22).

1.4 Vestibular Ocular Reflex

The VOR is a three-neuron pathway that transduces vestibular information to produce compensatory eye movement(23). Vestibular lesions disrupt the function of this reflex, leading to oscillopsia, dizziness and vertigo(24). Clinical assessment of this reflex can be used to test vestibular system function.

1.5 Vestibular Function Testing

Investigation of vestibular function requires the application of a vestibular stimulus and the measurement of the reflexive eye movements. Current tests include the head impulse test (HIT), calorics, rotational chair testing (RCT), Vestibular Evoked Myogenic Potential Cervical (cVEMP), Vestibular Evoked Myogenic Potential Ocular (oVEMP). The specificity and sensitivity of these tests in relation to unilateral and bilateral vestibular dysfunction differs. Much of the current literature supports the use of caloric testing in the assessment of unilateral vestibular dysfunction (25). As such it is considered the clinical "gold standard". Other measures have not consistently reached the same accuracy as calorics. It is possible that some of these limitations are due to their compatibility with the available eye recording equipment.

The induced eye movements are quantified by using recording techniques such as electro-oculography (EOG), video-oculography (VOG) or scleral search coil recording (SCCR). Electro-oculography is susceptible to eyelid flutters which induce a myogenic signal and electrical noise, this adversely effects the trace of

the eye movement. Until recently, video-oculography equipment was heavy causing slippage between the camera and the head during movement. This results in measurement artifacts, especially during head impulse testing. Newer, lighter VOG equipment has reduced these problems, both ease of use and portability mean that it is more clinically appropriate. Scleral search coil recording is painful and requires topical corneal anesthesia. Video-oculography shows comparable accuracy to SCCR, but there is a paucity of studies showing its utility in a clinical setting.

1.6 Cognition

Vestibular damage has been shown to lead to cognitive deficit and problems with spatial memory formation in animals and humans(26, 27). Given the significant links to the hippocampus this is likely to be in the form of spatial memory and spatial orientation(28-30). Better understanding of these mechanisms could lead to improved interventions and outcomes following vestibular lesions. Especially when applied in the context of vestibular function testing.

1.7 Aim

Using a comparative, observational design this study compares two measures of VOR function, vHIT and Calorics. It then relates the results of these tests to broader measures of patient function in vestibular schwannoma; audiometry, dizziness handicap inventory, tumour size and cognitive function. In doing so validating the accuracy of vHIT in comparison to calorics in quantifying VOR function, while highlighting their place in the clinical battery.

2. Literature Review

This literature review evaluates the clinical utility of each measure of vestibular function in relation to VS. First it describes normal vestibular function, and then summarizes different vestibular diseases before examining the utility of different testing methods, and their role in clinical decision-making.

Currently, quantitative vestibular function is not routinely performed in VS management, as such vestibular function tests contribute little to decisions about intervention. The slow growth of VS means that a "wait and watch" approach is becoming increasing popular in clinical management of many VS. Vestibular tests may be used to monitor changing vestibular dysfunction during this time that may be associated with increasing tumour size.

2.1 The Vestibular System

2.1.1 Vestibular Anatomy

Located in the temporal bone the vestibular system consists of a membranous structure bound by a dense bony case called the otic capsule. These are collectively known as the vestibular labyrinth, and described as either the bony or the membranous labyrinth (Figure 1). The outer membrane of the vestibular labyrinth is the endostium of the otic capsule and within this there are two fluid filled compartments. The perilymph compartment surrounds the endolymph compartment which is enclosed by a membranous sheath and which contains the sensory components of the vestibular system.

The membranous labyrinth consists of three semicircular canals (SCCs) and the otolith organs, the saccule and utricle. Each semicircular canal lies at right angles to the others and dilates at one end to form the ampulla. The sensory system within the vestibular labyrinth comprises the ampullary apparatus of

each semicircular canal and the otolith organs in the saccule and utricle. Contained in the ampulla are cristae, sensory epithelium supported by a connective tissue network, upon which the cupulae sit. These cupulae attach to the roof and lateral walls of the membranous labyrinth forming a closed barrier, stereocilia from hair cells on the cristae project into the cupula. The otolith organs consist of maculae made up of hair cells and supporting cells. Layered on top of this is the supracopula network, a mucopolysaccharide gelatinous layer embedded with the otoconia, small calcium carbonate crystals. The sacular macula lies on the anterior vertical wall of the saccule, while the utricular macula lies in the horizontal plane of the utricle.

Hair cells can be divided into type one inner and type two outer hair cells with each surrounded by a chalice of nerve endings (Figure 2). Stereocilia decrease in height with increased distance from a central kinocilium. Movement relative to the kinocilium allows for hyperpolarisation or depolarisation.

Figure 1: The Vestibular Labyrinth

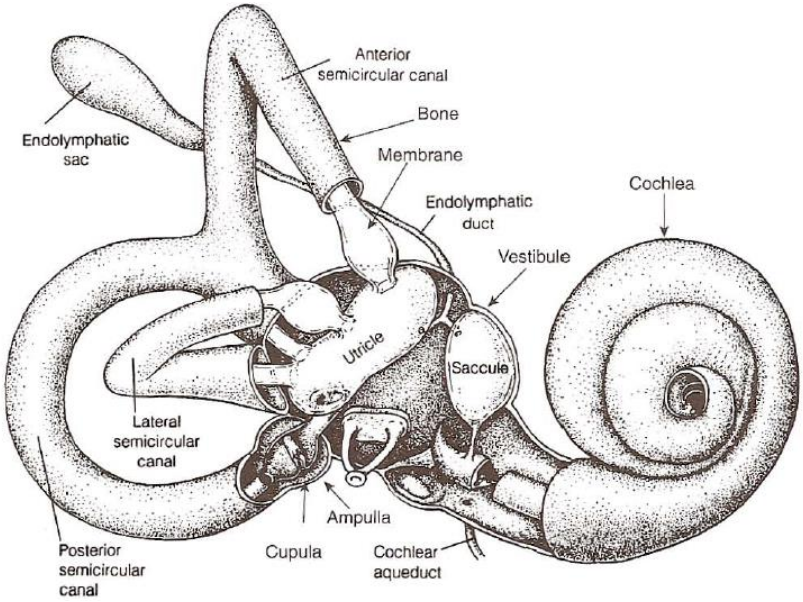

Figure 1 Legend: The vestibular labyrinth consists of the three semicircular canals and the otolith organs(1).

Figure 2: Vestibular Hair Cells

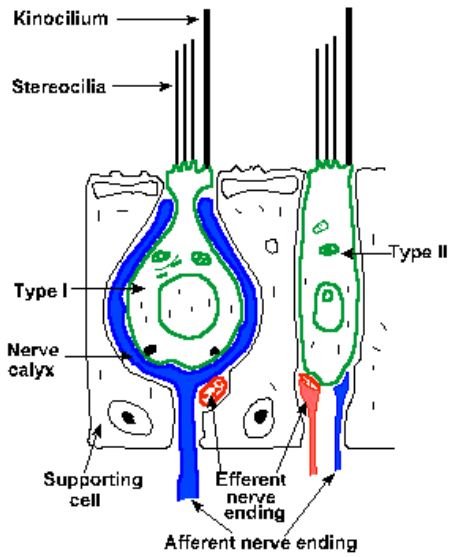

Figure 2 Legend: Movement of the stereocilia results in the transduction of signals to the vestibular nuclei(2)

Each organ generates a resting potential. Rotational movements modulate this via the SCCs. While horizontal or vertical movements modulate this via the saccule and utricle. These changes in signal, along with visual and proprioceptive information allows for the coordination of balance.

The external aspect of the membranous labyrinth is bathed in perilymph, with a high sodium to potassium ratio. The membranous labyrinth is filled with endolymph; this has a high potassium to sodium ratio. The charge difference between the two compartments generates an electrochemical gradient allowing for vestibular signaling. Endolymph is produced by the dark cells of the cristae and macule and reabsorbed into the endolymphatic sac via the utricular, sacular and endolymphatic ducts.

The labyrinthine artery (internal auditory artery) supplies the vestibular labyrinth(31). This normally arises from the anterior inferior cerebellar artery, but may also arise from the basilar artery.

Vestibular hair cells are surrounded by nerve endings. These are part of bipolar nerve fibres that have cell bodies located in Scarpa's ganglia, the latter situated within the superior and inferior divisions of the vestibular nerve. These afferent nerves fibres convey stimuli generated by hair cells of the vestibular nuclei. Nerve afferents from the superior canals, the lateral canals and the utricle run from Scarpa's ganglia in the superior vestibular nerve. While nerve afferents from the inferior canal and the saccule run in the inferior vestibular nerve (Figure 3). These along with the cochlear nerve make up the vestibular cochlear nerve. This runs through the internal auditory canal, along with the facial nerve and nervus intermedius, where it terminates in the vestibular nuclei at the level of the pontomedullary junction.

There are four main vestibular nuclei, the superior vestibular nuclei, the lateral vestibular nuclei, the medial vestibular nuclei, and the dorsal vestibular nuclei. Vestibular connections are varied, with nerve projections from the vestibular nuclei running to the cortex via the thalamus, the cerebellum, the spinal cord,

and oculomotor nuclei(32). Second order afferents arise in the medial and superior vestibular nuclei and run in the median longitudinal fasciculus to the abducens, trochlear and the oculomotor nuclei. The lateral vestibular nuclei largely supply fibres to the lateral vestibular spinal tract, while the medial vestibulospinal tract is largely supplied by the medial vestibular nuclei. There are some direct connections to the cerebellum, though second order afferents primarily arising from the medial and inferior vestibular nuclei to supply the cerebellum. Projections to the cerebrum primarily arise from the superior vestibular nuclei and run to the thalamus then to the cerebral cortex. The vestibular area is poorly defined; research suggests it may be adjacent to the auditory area or insula (33). The medial and inferior nuclei also give off connections to the cerebellum. These central connections are responsible for the integration of balance and the somatic responses seen when balance dysfunction occurs. There is evidence for direct connections between vestibular brainstem nuclei, forebrain and hypothalamic structures(34).

Figure Three: Vestibular Nerve Origins

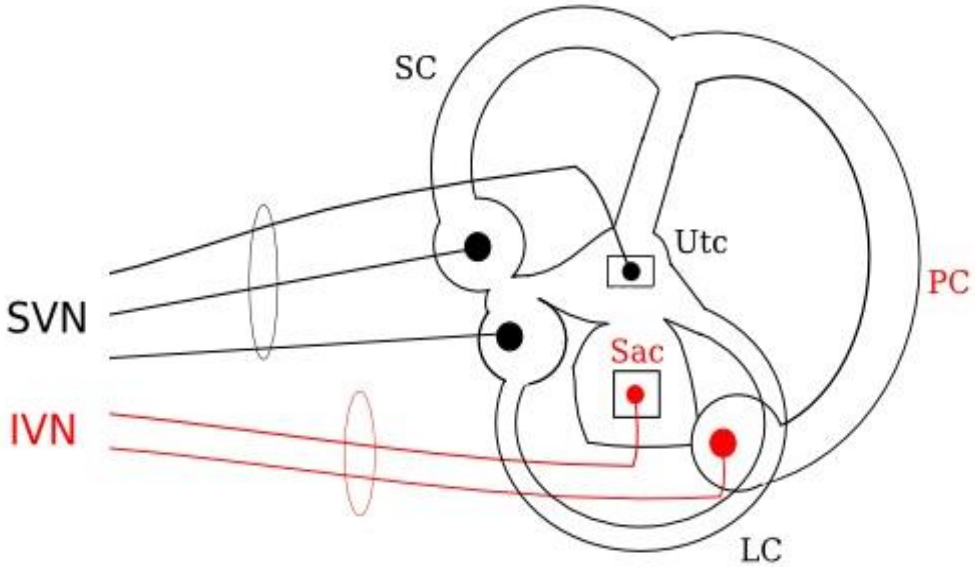

Figure 3 Legend: Innervation of the vestibular organ is by the superior and inferior divisions of the vestibular cochlear nerve (SVN and IVN). The SVN supplies the superior canal, lateral canal and the utricle. The IVN supplies the saccule and posterior canal. SC: Superior Canal, LC: Lateral Canal, PC: Posterior Canal, Utc: Utricle, Sac: Saccule

2.1.2 Vestibular Physiology

Angular acceleration results in endolymph inertia inducing cupula displacement, and consequent movement of the stereocilia relative to the kinocilium. Stereocilia are connected to each other and to the kinocilium by tip links attached in an axis towards the kinocilium, and directly open mechanically gated ion channels. A constant flow of potassium into the kinocilium generates a resting potential. As the cilia move the degree of tension present in the tip links moderates the opening of the ion channels, grading the degree of vestibular response. Increased movement causes the ion channels to open further allowing an influx of potassium ions from the endolymph depolarizing the cell. This opens voltage gated calcium channels; inflowing calcium binds to vesicles releasing glutamate into the intrasynaptic cleft activating the postsynaptic bouton, thereby generating a nerve potential.

Movement of the stereocilia towards the kinocilium results in depolarization and an excitatory signal. Movement away from the kinocilium results in hyperpolarization and an inhibitory signal as tip links are oriented towards the central kinocilium.

Acting as 'push-pull' pairs the paired contralateral SCCs generate information about rotational movement (Figure 4). In the context of the VOR the rate of discharge is influenced by the movement of the cupula in relation to the kinocilium. Rotational head movements produce opposite direction of cupula movement on each side and contrary alterations of discharge rate from the opposite paired SCCs.

The maculae act to detect gravitational or movements in the horizontal plane. Acceleration along one of these planes results in otoconia inertia and displacement of the supracopula network. This induces a cell depolarization, hair cell discharge and increased signal transduction along the vestibular nerve.

2.1.2.1 Vestibular Ocular Reflex

The VOR is a reflex mechanism that regulates gaze stabilization during movement(35). Signals from vestibular afferents are stronger when the head is rotated towards their respective side. Consequently the brain detects side-to-side differences. The summed hair cell activity from each vestibular end organ is conveyed via the vestibular nerves to the vestibular nuclei from here inter neurons pass to the contralateral abducens nuclei and rectus muscles via the median longitudinal fasciculus (Figure 4). Fibers also project from the vestibular nuclei to brainstem autonomic centers, via the cortex and vestibulospinal tract. This process results in compensatory and contralateral eye movements in response to horizontal head rotation stabilizing gaze. This reflex operates physiologically during head movements between one to six hertz. Above this frequency visual acuity is lost, while at lower frequencies other mechanisms can compensate.

During constant head movement, the neural firing rate in the vestibular nerve decays at an exponential time constant of five to six seconds. Central velocity storage mechanisms extend the vestibular time constant out to around 20 seconds, this is the mechanism underlying post rotatory nystagmus. Visual input increases vestibular dumping, reducing post-rotatory nystagmus(36).

The vestibular ocular reflex is moderated in the cerebellum by the floculus and the nodulus (37, 38). The floculus calibrates the VOR gain. Following a lesion to the floculus animals show diminished ability to adapt to disorders that increase or decrease VOR gain (39). The nodulus moderates the duration of VOR responses (40).

Gain, phase shift and asymmetry are all quantifiable measures of the VOR. The VOR gain is the ratio of the angular eye movement over the angular head movement, measured either in velocity or in change of angular position. As compensatory eye movements should be of equal magnitude but opposite direction to head movements, perfect gain is equal to one. There is not yet

accepted cut-offs of abnormal function due to insufficient data, but young, healthy adults have a gain approaching 1.0.

2.1.2.2 Role of Inhibitory Interneurons

The vestibular nuclei are connected by commissural neurons. Each vestibular nucleus receives information from the paired semicircular canals (Figure 5). This information is integrated via commissural neurons to produce information regarding the orientation of the head in space(41).

The commissural system is reciprocal, and functionally inhibitory(42). Second order inhibitory neurons run directly between the paired vestibular nuclei. Inhibitory neurons in the vestibular nuclei also receive excitatory input from the other contralateral vestibular nuclei. Consequently each vestibular nucleus can inhibit the other.

Figure 4: Vestibular Ocular Reflex Arc

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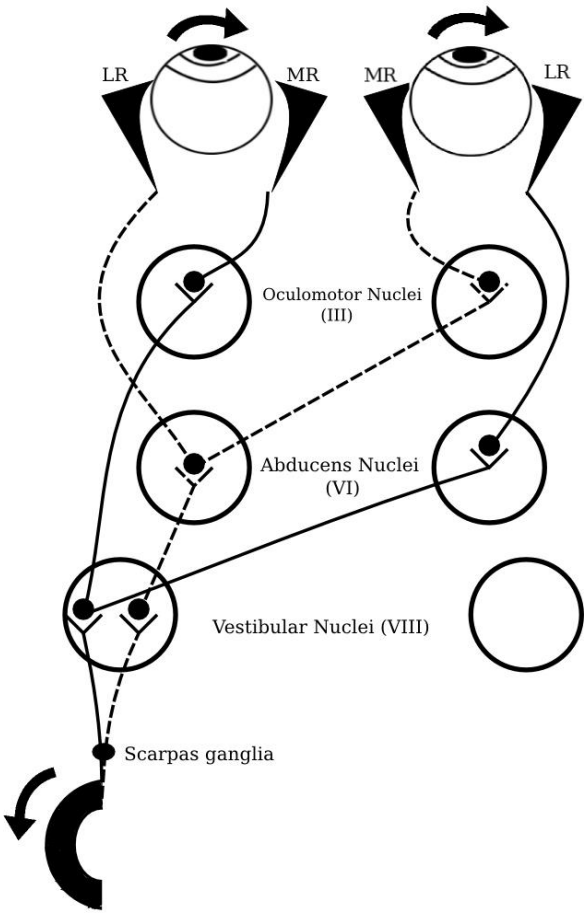

Figure 4 Legend: Vestibular Ocular Reflex Arc: Excitation of the left lateral canal by left sided rotation results in endolymph inertia and resultant cupula displacement. This results in eye movements of equal magnitude in the opposite direction.

The response in the right lateral canal is the inverse of that depicted above. Solid Lines indicates the excitatory signals, Dotted indicates the inhibitory signals
LR: Lateral Rectus, MR: Medial Rectus

Figure 5: The Paired Semicircular Canals

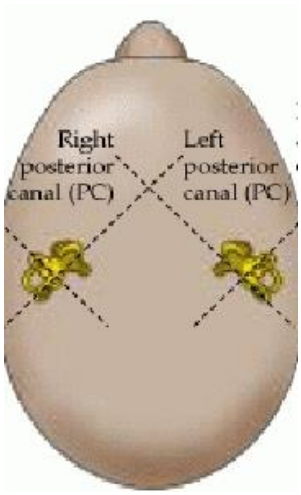

Figure 5 Legend: The contralateral lateral SCC act as a functional pair, as do the contralateral posterior and superior canals(3).

2.1.2.3 Vestibular Compensation in Unilateral Vestibular Deafferentation

Vestibular compensation is a complex multifactorial process believed to be reliant on both cortical and subcortical processes. This process includes adaptive changes in both synaptic and neuronal pathways (43). Several authors have highlighted the impact of unilateral vestibular deafferentation on the ipsi and contralateral vestibular nuclei resulting in vestibular ocular defects(44-46). The vestibular nuclei roles in modulating efferent and afferent output have lead to the investigation of their role in vestibular plasticity.

The work of Precht et al(47) first highlighted the importance of the vestibular commissural system on vestibular compensation. Following unilateral vestibular deafferentation (uVD) the ipsilateral deafferented vestibular nuclei is known to become "quiet", while the contralateral vestibular nuclei remains either normal or becomes hyper excitable due to decreased inhibition from the contralateral "quiet" vestibular nucleus. The hyper-excitable contralateral nuclei can then further inhibit the ipsilateral deafferented nuclei due to decreased inhibition from the "quiet nuclei". It is this imbalance in vestibular outputs that can lead to functional consequences, such as a disrupted VOR and dizziness. Normal vestibular function is restored as inhibitory potentials from the normal nuclei are reduced. This effect was by highlighted by Vibert et al(48)who found no change in vestibular potentials 1-2 days post trauma, but decreased potentials at days 3-4. When bilateral vestibulectomy was performed decreased vestibular firing rates were found bilaterally, but no vestibular signs or symptoms were present(49).

This highlights that it is the imbalance of vestibular information between the relative nuclei that leads to symptoms. With time the vertigo associated with unilateral hypofunction diminishes because of adaptive changes along with central nervous system supplementation.

The commissural system may be moderated by the inhibitory neurotransmitter gamma-Aminobutyric acid (GABA). A clear pathway has not been shown but changes in GABA and GABA receptor action are seen post deafferentation. Two in vitro studies have shown that following deafferentation the functional capacity of GABA-A and GABA-B receptors was down regulated in the ipsilateral nuclei (48, 50). It is believed that this is to reduce the response to contralateral inhibitory input and expediting vestibular compensation. Both histamine production and stress hormones may have a role to play in the modulation of GABA release post uVD(51). Their role has yet to been clearly outlined.

2.2 Vestibular Pathology

2.2.1 Vestibular Schwannoma

2.2.1.1 Presentation and Diagnosis

Vestibular schwannoma are a benign, slow growing tumour of the vestibulocochlear nerve. They comprise around 6% of all intracranial neoplasms(52). Vestibular schwannoma usually present with hearing loss but can also cause vestibular hypofunction in the affected nerve, disequilibrium, and vertigo. The compromise of bloody supply and mass affects has been proposed as a mechanism of audio-vestibular dysfunction.

Presenting symptoms can include unilateral hearing loss (99%), tinnitus (63%), dizziness (40%), facial or trigeminal nerve signs (8%) and lower cranial nerve signs (3%)(53). Magnetic resonance imaging (MRI) is used to make definitive diagnosis. The clinical work up normally includes pure tone audiometry, speech discrimination testing. Even though a large proportion of VS patients suffer significant balance disturbance vestibular function is not routinely monitored as part of the clinical workup. Due to their slow growing nature conservative management using the watch and wait strategy has become popular in recent

years, with patients undergoing repeated MRI scanning to monitor for schwannoma growth. One study found that that up to 57% of tumours did not grow during the study periodand among those that did grow the average rate was 1.9mm per year (54). When there is tumour growth either surgery or radiotherapy may be recommended. A number of variables may influence treatment choice, for example; age, general health, tumour size and patient preference.

2.2.1.2 Aetiology

Currently the aetiology of unilateral VS is unknown. . There is conflicting evidence about the impact of cell phone use on the development of vestibular schwannoma(55-58)

2.2.1.3 Pathophysiology

It is believed that the inactivation of the Neurofibromatosis type 2 (NF2) gene, located on chromosome 22 is involved in the pathogenesis of both sporadic unilateral and familial VS (59, 60). Irving et al demonstrated that inactivation of both copies occurred in familial and sporadic VS, suggesting that the NF2 gene acts as a tumour suppressor (61). Welling (62) found NF2 mutations in 66% of sporadic VS patients, though only 88% of the coding sequence was screened. Additions on chromosome 9p and 17q have been found in some tumour samples (63). This indicates that NF2 mutation may not be the only precipitating factor in the development of sporadic VS, while further highlighting the complex genetic nature of its pathogenesis

The NF2 gene produces schwannomin, a protein that plays a role in linking cytoskeletal components to the plasma membrane(64). It is believed that schwannomin has a role in maintaining cytoskeletal organization, with increased disorganization seen in VS(62). In doing so schwannomin may act to limit cell motility, thus inhibiting excessive tumour growth(65). Indeed ga the introduction of schwannomin through a viral vector has been shown to decrease

in vivo growth of VS cells, with increased apoptosis(66-68). It is believed that this mechanism may be under control of external moderators with the loss of the schwannomin protein resulting in the inability to appropriately respond to these external growth cues (69). These studies highlight the importance of the NF2 gene mutations and schwannomin production in the pathogenesis of vestibular schwannoma, and raise the possibility of genetic treatment.

It has been speculated that erythropoietin (EPO) plays an important role in the development of the human central nervous system(70). Using a recombinant antibody one study found positive staining for EPO in 93% percent of schwannoma cell cytoplasm, and 63% of endothelial cell cytoplasm(71). Falconi (72) also reported the presence of a fast growing vestibular schwannoma requiring surgery in a patient treated with EPO. Tumour size has been correlated with the number of vessels present around the tumour capsule as well as the degree of blood extravasation(73). Taken cumulatively these results indicate that EPO plays a role in tumour growth and vascularity.

2.2.1.4 Epidemiology

The average age at diagnosis ranges between 59-62 years(74). The reported incidence of vestibular schwannoma has ranged from 0.1/100000 per year to 2/100,000 per year(74-77). Histopathological studies in cadaveric temporal bones have demonstrated an incidence of 0%-2.7% (78, 79). With the 2.7% rate likely to be an overestimation due to selection bias, as this would indicate an incidence of around 800/100,000 per year. In recent years the increased prevalence of vestibular schwannoma is largely attributed to the increased detection of small intrameatal tumours showing few symptoms by MRI (74). This has been mirrored by a significant decrease in the number of large tumours diagnosed, with studies showing a decrease in diameter from 35mm in 1979 to 10mm in 2001(76, 80).

Vestibular schwannoma can be classified as intra or extrameatal. Growth in intrameatal tumours is measured by taking the longest length along the

intracannalicular space. Extracannalicular tumours are measured according to the largest extrameatal diameter. With extracannalicular tumours classified as small 1-10mm, medium 11-20mm, moderately large, 21-30mm, large 31-40 mm and giant 40+ mm(81).

2.2.1.5 Growth

Vestibular schwannoma show inconsistent growth rates with some growing continuously, others growing and stopping while yet others may grow and shrink(74). With Stangerup (76) showing that of the tumours that did grow the majority did so within the first five years following diagnosis. A recent systematic review found that during a 38 month period 46% of tumours grew while 8% regressed(74). Observational studies tracking tumour growth rates may be subject selection bias as young people with large tumours, and middle-aged people with medium size tumours are more likely to undergo surgery, producing an overabundance of small tumours in studies (76). No correlation has been found between growth rate, sex and age.

Deterioration of PTA and speech discrimination scores are not correlated with increasing tumour growth and hearing is known to deteriorate regardless of where tumour growth occurs (82). This highlights the limitations of pure tone audiometry and speech discrimination scoring as a functional monitoring procedure (60).

2.2.2 Other Vestibular Disease

2.2.2.1 Benign Positional Paroxysmal Vertigo

Benign paroxysmal positional vertigo (BPPV) is characterised by sudden attacks of extreme vertigo lasting less than a minute. Light-headedness, nausea and imbalance may also be experienced. It commonly presents between the ages of 50-70 years, with a yearly reported incidence between 10.3/100,000 and 17.3/100,000 people (83). The majority of BPPV cases are believed to be

idiopathic though some may be caused by trauma. Benign Paroxysmal Positional Vertigo is caused by small free-floating particles believed to arise from dislodged otoconia, known as canalolithasis. Over time these particles will accumulate to form a critical mass. Head movement then results in cupula displacement due to inertia of these dislodged otoconia particles, the consequence of which is inappropriate activation of the vestibular apparatus leading to vertigo. Due to its inferior position and gravity effects the posterior semicircular canal is most commonly affected.

Attacks may occur in frequent spells over the course of a week, before repeated movement breaks up the canalolithasis. The diagnosis is made on the basis of history and clinical examination, including the Dix Hallpike maneuver. The standard maneuver involves quickly moving the patient from a seated to lying position on the examination bed holding the head such that the head is moved in the axis of the left or right posterior canal. A positive Dix Hallpike occurs when torsional nystagmus is produced, with a less marked up-beat component towards the affected ear, this is reversed on sitting up. The most cases are self-limiting and resolve within six months. Treatment options include vestibular habituation exercises and physical therapy such as the Epley manoeuver. Obliteration of the affected SCC has been proposed for intractable cases.

2.2.2.2 Meniere's Disease

Meniere's disease is a condition that commonly presents with fluctuating hearing loss, aural fullness, tinnitus and vertigo not lasting more than 24 hours. It presents primarily between the ages of 40-60 years, with a reported incidence of between 15/100,000 and 157/100,000 people per year (84). Nystagmus may be present during attacks, often persisting for several days. Initially this beats towards the affected ear, before reversing and beating towards the unaffected ear. This reversal may repeat, therefore direction of nystagmus cannot be used to accurately identify the affected side; it is believed that this may be due flow of potassium ions across ruptures in the membranous labyrinth which separates the endolymph and perilymph compartments. The current aetiological origin is

unknown, with the exact pathophysiology controversial. Current beliefs hold that a key pathological component is the formation of endolymphatic hydrops; this may be idiopathic or due to infection, trauma or allergens. Hydrops can be due to overproduction or inadequate removal of endolymph leading to distortions of the endolymphatic membrane. Mechanical disturbance due to hydrop expansion can lead to destruction of some parts of the membrane resulting in mixing of endo and perilymphatic fluids. The consequence of this is inappropriate excitation and inhibition of the vestibular organs as well as the organ of Corti producing patient symptoms. Treatment is varied and decided on a patient-to-patient basis. In very mild cases a low salt diet may be suggested. As severity of symptoms increases diuretics or vestibular sedatives such as betahistine for acute attacks may be used. In very severe cases a stent may be inserted to decrease intratympanic pressure (85, 86). In intractable cases ablation with an aminoglycoside such as gentamicin or surgery may be indicated.

2.2.2.3 Vestibular Migraine

Vestibular migraine can present with spontaneous positional vertigo, dizziness, ataxia, frequently with no relationship to headaches. Typically attacks last minutes to hours (87). Currently the pathophysiology has not been established. Patient monitoring during episodes has suggested that a mixed central peripheral cause in the pathogenesis is culpable (88, 89). Intervention can include non-pharmacological methods of control with avoidance of triggers such as poor sleep hygiene, reactive foods, and dehydration. In more severe cases a prophylactic treatment may be required. This may include a vestibular sedative or anti-migraine medication including beta-blockers, calcium channel blockers or a tricyclic antidepressant.

2.2.2.4 Vestibular Neuritis

Vestibular neuritis presents with a severe attack of vertigo developing over several hours lasting up to days but easing over a period of several weeks(90). This may be coupled with non-specific dizziness and imbalance. The median age

of presentation is 41, with an incidence of 3.5/100,000 people per year (91). The etiology is unknown, but some cases may be due to latent type 1 herpes simplex infection of the vestibular nerve(92, 93).

Clinical testing normally shows spontaneous peripheral nystagmus, and positive head impulse test towards the affected side. The Romberg test may also be positive. The affected side also frequently shows little response to caloric stimulation.

Treatment is currently focuses on reducing the severity of the vertigo symptoms rather than dealing with the underlying cause. H1 receptor antagonists including promethazine, and benzodiazepines including lorazepam are frequently used. Corticosteroids such as prednisone have also been used in an effort to reduce inflammation and modify the clinical course.

2.2.2.5 Bilateral Vestibular Failure

Gentamicin over dosing is the most frequently identified as the cause of bilateral vestibular failure. Meniere's disease can also lead to bilateral vestibular failure when both inner ears are affected. Typical presenting symptoms include oscillopsia, and balance disturbance. The diagnosis is most frequently made on the basis of clinical examination and reduced caloric response. Treatment options are limited though vestibular function exercises should be recommended.

2.2.2.6 Non-Vestibular dizziness

A wide variety of non-vestibular dizziness exists, with the distinguishing feature often the absence of vertigo. Indeed non-specific dizziness such as presyncopal light-headedness frequently is seen in anemia, hypoglycemia and other cardiorespiratory conditions. Extreme anxiety and panic attacks can also lead to dizziness. While central neurological conditions such as cerebellar disease or multiple sclerosis can lead to gait imbalance.

2.3 Vestibular Testing

2.3.1 Assessment of Ocular Responses

Traditionally clinical assessment of vestibular function has relied on observation of eye movements, either using the naked eye, Frenzel Glasses, or by video-nystagmography. During caloric testing the induced nystagmus is usually easily observed by the naked eye without eye recording, but the end point can be difficult to define. During head impulse testing overt catch-up saccades are sought, however, smaller catch-up saccades may occur during the head impulse and these may not be seen. Consequently, naked eye observation of the VOR has low sensitivity and high specificity, although sensitivity can increase with examiner experience(94)(Table 1).

2.3.2Electro-Oculography (EOG)

Electro-oculography (EOG) utilises the standing corneo-retinal potential to quantify eye movements; the cornea carries a positive charge relative to the retina, creating a dipole(95). Recording electrodes are placed at the outer canthus of each eye, and an earth electrode is placed on the forehead. Horizontal eye movement brings the positive cornea into closer proximity to either the temporal or nasal electrode inducing a change in voltage between the electrodes, quantifying nystagmus produced by caloric or head impulse stimulation(96, 97). Measuring the movement of both eyes improves the signal to noise ratio, increasing recording accuracy(98). Electro-oculography can take place in conjunction with video recording to allow for clinician observation of eye movements(99).

2.3.3 Video-Oculography

Video-oculography uses goggle-mounted high sample frequency infrared cameras to record eye movements, either through identification of iral landmarks, or by pupil contrast(100-102). A rotation vector analysis allows for 3-dimensional measurement(103). The accuracy of VOG technology has been validated in comparison to the gold standard scleral search coil recording(104, 105).

2.3.4 Scleral Search Coil Recording

Scleral search coil recording is considered the gold standard for laboratory based eye movement recording(104, 105). Metal coils are embedded in annular contact lenses and placed over the participant's pupil. The subject is placed in a magnetic field; eye position is then deduced from the amplitude of the current induced in the coil by the magnetic field. Accuracy is excellent, with extremely high spatial ($<<1^{o}$) and temporal resolution (<<1ms) (105). Movement can be also characterised in the horizontal, vertical and torsional plane. SCCR is rarely used in the clinical setting, as it requires a specialized laboratory, and is not well tolerated. The cornea has to be anesthetised and the coils can only remain in place for a limited amount of time.

2.3.5 Vestibular Testing Techniques

2.3.5.1 Caloric Testing

Caloric reflex testing with eye movement recording has long been considered the clinical gold standard for investigation of vestibular hypofunction. In 1906 Barany(106) proposed that caloric induced convection currents lead to gravity induced endolymph movement and consequent nystagmus. Later studies indicate that his conclusions are likely to be accompanied by other factors (107). However, temperature induced convection currents are still considered the primary underlying physiological event(108).

The Fitzgerald and Hallpike bi-thermal caloric test, devised in 1942, which employs two water temperatures (30°C and 44°C) is in common clinical use today(109). Prior to their study the procedures employed for this examination were variable and many caused patient discomfort. This included multiple irrigations using graded temperatures, at extremes from normal body temperature. Fitzgerald and Hallpike believed that the test needed to be practical and able to identify small changes in the reflex mechanisms. They concluded that the stimulus should be small to restrict excitation to the lateral canal and chose hot and cold stimuli of close equidistance to body temperature so that small differences in the reflex mechanisms could be identified. Their recommended method involves irrigating the external auditory meatus of each ear with cold (30 °C) and warm (44 °C) water alternately. Caloric stimulus is equivalent to rotational input of 0.02-0.04 Hz (110, 111). Normally the physiological range of the VOR is between two and six HZ(112).

Initially the duration of the induced nystagmus was timed, this allowed canal paresis and directional preponderance to be roughly derived(113). The advent of electro-oculography allowed direction and speed of slow phase nystagmus to be measured. Jongkees utilized this information to create formulae for canal paresis, $\frac{(WR+CR)-(WL-CL)}{WR+WL+CR+CL} x100$, and directional preponderance (DP)(114).

The sensitivity of calorics in identifying vestibular hypofunction in unilateral VS has ranged from 50-100% depending on tumour size(115). As it is considered the "clinical gold standard" studies assessing new vestibular tests are compared to calorics. To date newer testing modalities have failed to consistently achieve equivalent accuracy.

Incomplete ear irrigation can produce diminished responses. Calorics may induce nausea, vertigo and migraine. Testing may not be possible on those with tympanic membrane perforation, or recent ear surgery. Controlling temperature and flow rate requires equipment that may not necessarily be available at the

bedside. Order effects with cool and warm irrigation have been raised; however, there is no indication that this introduces significant systematic bias (116).

Mono-thermal testing has been shown to have lower sensitivity than bi-thermal testing but takes less time and reduces patient discomfort (117-119). Air caloric testing using either moist or dry air is comparable to bi-thermal calorics in normal individuals(120); however, the technology is not widely available and data in disease is not yet available.

Calorics can be utilized as a measure of VS progression. Tumour sizes exceeding 20mm in diameter have been correlated with decreasing labyrinth excitability(121). However, no studies relate this to patient function or quality of life measures. This is important as the degree of 'vestibular compensation' and functional recovery varies between individuals(44).

2.3.5.2 Examiner Induced Head Impulse Testing

Head impulse testing is an established measure of the high velocity VOR. Halmyagi's (122) seminal study showed 100% sensitivity and specificity in detecting complete canal paresis in patients following unilateral vestibular neurectomy. Examiner driven head rotation to one side induces endolymph movement, which deforms the cupula of both lateral semicircular canals. This induces both a contralateral inhibitory and an ipsilateral excitatory response along the vestibular nerve to the vestibular nuclei. In patients with a unilateral deficit the diminished response from the ipsilateral affected side and saturation of the contralateral inhibitory response leads to a failure of the VOR and a catch-up saccade. Testing with a high frequency, short rotational stimulus ensures no overlap with other visuo-vestibular pathways.

Catch-up saccades can be recorded using video-oculography and quantified in terms of gain. The lack of sufficient comparable data precludes definition of accepted parameters for abnormal gain. Small data sets indicate normal gains range from 0.74-0.96 in healthy subjects (94, 123, 124). Gains fall to around 0.25

following unilateral vestibular neurectomy, in comparison to 0.8 on the intact side(125). Gain asymmetry has been suggested as a method for quantifying abnormal VOR function, with one study indicating normal asymmetry to be less than 5.6% (123). To quantify test results the examiner can use VOG or SSCR. Both systems export head and eye movement recording to a computer allowing for the calculation of gains.

In clinics head impulse testing is often performed without quantification. Patients are instructed to sit facing the examiner who then grips the patients face, with thumbs on the zygomatic bone, fingers reaching around onto the mastoid process and occipital bone. Patients are then instructed to "fixate on the point located in front of you" (often the examiners nasion) while I turn your head to each side". The examiner then turns the patient's head to one side the patient's head, aiming for rotation velocities of above 150 °/s. The presence of overt catch up saccades indicates vestibular hypofunction.

To quantify test results the examiner can use VOG or SSCR. In VOG the patient wears video goggles. The examiner is located behind the patient and, and the thumbs are placed on the occipital bone, and the forefingers on the zygomatic bone. When using SSCR the patients' eyes must first be anaesthetized before the search coils, imbedded in contact lenses are placed over their eyes. Both systems export to a computer recording head and eye movement allowing for the calculation of gains.

Head impulse testing is useful for identifying a unilateral vestibular deficit(126, 127). Studies of such patients have shown consistent sensitivities of between 34% and 39% when compared to calorics(128). A canal paresis of greater than 60% is often required for a positive HIT, with sensitivity increasing to 87% in the presence of a 100% paresis(111, 128). These studies corroborate the high specificity (100%) described by Halmagyi and Curthoys(122). The low sensitivity (34-39%) and high specificity (100%) of HIT may be a consequence of how it is quantified. Clinical observation alone cannot detect covert saccades or quantify gain. While EOG measurements may be subject to muscular and

blinking artifacts. The physician's hands may also interfere with electrode recording. Horizontal resolution is limited to one degree(129). Until recently eye movement velocity and camera size limited the utility of video HIT. New systems such as the have overcome these problems. Accuracy in comparison to SSCR has been validated(104, 130, 131).

HIT without video-oculography is well validated but reactive saccades indicating vestibular hypofunction may occur during the head movement. These covert saccades cannot be picked up through observation alone, and video recording is required to maximise test sensitivity. However, expense, difficulty of use and patient comfort has limited their clinical use.

Ulmer et al (132) recently identified abnormal gains in the majority of patients with a canal paresis greater than 40% using HIT with VOG. These results highlight potential as an alternative to the calorics. Evidence is lacking with regard to the use of HIT in VS; that available is mostly observational studies with small sample sizes, investigating other types of vestibular lesions(133-135).

2.3.5.3 Patient Induced Head Impulse Testing

Active head impulse testing (Active-HIT) uses voluntary head rotation, aided by auditory cues. It activates the high velocity VOR using the same mechanisms as passive head impulse testing. Eye movements are measured by either EOG or VOG and movement sensors characterise head movement. The data acquired is used to derive VOR gain and phase shift, characterizing vestibular dysfunction. Several studies have highlighted the accuracy of Active-HIT in normal subjects; though test-retest reliability has been questioned. As the movements are patient driven, both anticipation and muscle activity (myogenic responses) influence the responses recorded.

During active HIT patients are seated and instructed to fix gaze at a point ahead, before actively rotating their head from side to side; audio cues guiding head rotation frequency. These cues allow the VOR to be tested at various

frequencies. Eye movements are measured by either electro-oculography or video-oculography systems and movement sensors characterize head movement. This data is used to quantify the gain and phase shift of the VOR so characterizing vestibular dysfunction.

Strengths of active HIT include the lack of examiner input. This minimises goggle slippage and associated movement artifact. Also, compared to RCT it is cheaper and more portable. However,one concern is the patient's capacity to generate sufficient head movement frequency, though Hervonen et al(136) have shown that 94% of patients can achieve a rotational speed of 4Hz and 78% can reach up to 5 Hz. It has been suggested that patient anticipation and activation of concurrent myogenic responses may enhance the gain, especially during rotations below 2 Hz (137). Compared to calorics, lower sensitivity and specificity is reported(132). While, feed forward motor planning from active head movements via the premotor cortex and the frontal eye fields may initiate eye movements increasing gain through non VOR mechanisms(138).

Testing of VS patients post surgery showed significantly different gains between ipsilesional and contralesional sides(139). However, in another study only 58% of patients showed abnormal gain(140). Lower sensitivity when compared to calorics indicates that Active-HIT is a poor stand-alone measure of vestibular hypofunction. No studies were found that described utility in preoperative clinical management of VS.

2.3.5.4 Rotational Chair Testing

Rotational Chair testing was pioneered by Barany in 1907(141). Patients are secured in a chair designed to rotate at set frequencies; the stimulus may be sinusoidal or impulsive. The stimuli induce endolymph flow and cupula displacement activating the VOR. Rotational chair stimuli are limited to around 1 Hz. The resulting compensatory eye movements are measured using EOG or VOG. This information can then be used in conjunction with the chair angular

velocity to calculate the gain and phase shift, which is then used to quantify vestibular dysfunction.

Rotational chair testing allows for passive activation of the VOR. Patients are strapped into a chair designed to rotate at set frequencies; the stimulus may be sinusoidal or impulsive. The stimuli induce endolymph flow and cupula displacement activating the VOR. The resulting compensatory eye movements are measured using VOG or EOG. This information is then used in conjunction with the chairs angular velocity to calculate the gain or phase shift (timing of eye movement in relation to head movement). Vestibular dysfunction can then be quantified.

Rotational chair testing is considered the clinical gold standard for characterizing bilateral vestibular hypofunction(25). This is because both labyrinths are tested simultaneously and higher rotation frequencies can be employed. It has been shown to have greater specificity than but similar sensitivity to calorics (142, 143).

Although well validated(25), the equipment is expensive, RCT is not portable and requires a large room area. Consequently, it is often only available to specialized vestibular centers.

Rotary chair testing stimulates both vestibular labyrinths simultaneously; as most VS are unilateral they are often better evaluated by tests that stimulate each side separately. A recent study has suggested that "off vertical" axis rotations may be useful in investigation unilateral VS(144).

2.3.5.5 Vestibular Evoked Myogenic Potentials

Characterized as early as 1958, sound evoked myogenic potentials have been localised to the vestibular system(145, 146). These potentials are lost when the vestibular nerve is sectioned but remain present among those with sensorineural deafness(147). Either clicks or high frequency tones are conveyed

to the vestibular system by air or bone conduction, the latter is more reliable because any conductive hearing loss is circumvented. This activates the vestibular system, inducing a reproducible myogenic response in the cervical, and extra-ocular muscles. The cervical vestibular evoked myogenic potential (cVEMP) and ocular vestibular evoked myogenic responses (oVEMP) may be distinguished by recording activity in either the sternocleidomastoid (SCM) or oculomotor muscles. It is now generally considered that cVEMP is of saccular origin and oVEMP of utricular origin as the cVEMP is reduced following inferior vestibular neuritis, while the oVEMP is reduced in superior vestibular nerve lesions(148-150). The oVEMP is mediated via the VOR whereas the cVEMP is via vestibular-colic pathways(151). The oVEMP has a characteristic N1-P1 waveform, with N1 at about 10ms and P1 at about 15ms; the waveform is described as n10-p15. The cVEMP has a P13-N23 waveform that peaks at 13ms and 23ms.

As the cVEMP is an inhibitory response the SCM muscle has to be active; to achieve this, the subject either raises their head off the pillow or turns their head to the non-test side. In contrast, oVEMP is an excitatory response and the eyes may be at rest during recording, but this response appears to be best recorded from the inferior oblique muscle with the subject looking upwards.

VEMP dysfunction can be characterised by the presence or absence of response, calculating the asymmetry ratio between the amplitude of potentials generated from both ears (analogous to canal paresis in caloric testing), or comparing response latency.

When measuring cVEMP the subject lies on a bed, surface electrodes are then placed on the SCM muscles. An earth electrode is placed on the sternum and reference electrodes on the clavicles. As the cVEMP is an inhibitory response the SCM muscle has to be active and the subject must raise their head forward. High intensity clicks (100dB-145dB) or induced vibrations (500HZ) are then presented to the test ear(148, 152). A reproducible inhibitory waveform is then recorded via the electrodes; called the p13-n21, waveform(153). To measure the

oVEMP surface electrodes are placed around the extra ocular muscles. As this is an excitatory response the eyes may be at rest. Ocular VEMP produces a characteristic n1-p1 waveform(151).

Due to the new nature of VEMPs varying methodologies across studies mean that results are not readily comparable. Test results may be influenced by the degree of tonic neck muscle activation or gaze direction(152, 154). This is difficult to maintain at constant levels. A recent study has shown the capacity of cVEMP to identify vestibular dysfunction, with patients suffering from vertigo being more likely to have absent cVEMP compared to the control group(155).

There are few studies of VEMPs in patients with VS. Abnormal oVEMP have been reported in 70% to 80% of VS patients, as few as 37.5% of patients in one study(147, 148, 156). Chiarovano (152) identified abnormal oVEMP in nine of 12 patients, but only 50% had an abnormal cVEMP; there was weak correlation with canal paresis. However, despite this the mean waveform latencies were not significantly different from normal. This suggests that while oVEMP is potentially superior for monitoring VS, it still has limited usefulness.

Several studies have shown no significant difference between calorics and VEMP when investigating for VS, both tests showing a sensitivity of 80.8%, but specificity was only 52.7%(157). Test sensitivity is affected by the stimulus used with bone conduction showing a 15% decrease in sensitivity relative to air conduction(148).

Table 1: Sensitivity and Specificity for different vestibular testing modalities in identifying vestibular hypofunction in patients with vestibular schwannoma

	Sensitivity	Specificity
Calorics	69% 100%(113) 82%(158)	
Monothermal Calorics (Relative to bi-thermal Calorics)	30^0 C: 86%(117) 44^0 Cs: 82%(117)	30^0 C: 80%(117) 44^0 C: 78%(117)
HIT without VOG	Unilateral vestibular neurectomy: 100%(122) Dizziness: 35%(111) Vestibular hypofunction (42/150 patients with VS): 34%(128) Hypofunction in severe paresis: 87.5%(128)	Unilateral vestibular neurectomy: 100%(122) Dizziness: 95%(111) Vestibular hypofunction (42/150 patients with VS): 100%(128)
oVEMP	80.8%(159) 75%(156) 75%(152) 61.5%(148)	50%(159)
cVEMP	37.5%(148) 69%(156) 50%(152)	

2.3.6 Other Tests in Vestibular Schwannoma

2.3.6.1 Dizziness Handicap Inventory

The Dizziness Handicap Inventory (DHI) comprises 25-questions that aim to relate patients' perceived handicap for everyday tasks due to vestibular disease. Patients are administered the 25 questions by the examiner. It needs to be clearly outlined that the questions should only be related to dizziness, rather than other functional handicaps.

The DHI can be broken into three sub categories assessing physical, emotional and functional capacity. Each question is answered yes, sometimes, or no. Responses are scored 4, 2, or 0 respectively giving a total possible score of one hundred. A total of less than 25 indicate around 12 or fewer balance disturbances per year. A score between 25 and 34 indicates greater than 12 non-continuous balance disturbances throughout the year, greater than 49 indicates near continuous balance disturbance. In the seminal study it showed good internal consistency, test retest reliability was high and mean DHI score increased with increasing dizziness(160). Further studies have shown that DHI correlates with some balance function measures(161). The DHI allows for the assessment of the functional impact that dizziness has on a patient's life. This can inform clinical decision-making.

Principal component analysis of the DHI subcategory called into question their validity as individual measures (162). This should be taken into consideration when using subcategories to highlight a particular area of patient morbidity.

Wagner et al found no correlation between DHI scores and tumour size in patient's vestibular schwannoma(163). Though women were found to have significantly higher DHI than men, with 75% of patients having some degree of functional impairment. It is worth nothing that this study includes the intrameatal portion of the schwannoma when measuring its size. A further study reported the median preoperative DHI score to be 30, with age not a significant

factor in determining DHI scores(164). Another study found that for schwannoma less than 20mm diameter, the median DHI was 32, but in tumours large than 20 mm the median DHI was 20(162). The DHI could not be predicted from tumour size but the degree of preoperative canal paresis could be used to predict DHI outcome following surgical intervention(163).

Tumor size, sex, and magnitude of preoperative canal paresis significantly influence the degree of change in DHI following surgery. Age, the presence of central vestibular system abnormalities, and the nature of the patient's principal presenting symptom have no effect on DHI score following surgery. Use of the DHI in preoperative monitoring allows for assessment of schwannoma vestibular impact on quality of life. This is important as vertigo and dizziness strongly affect quality of life. Balance disturbance is the most significant audio vestibular predictor of quality of life in patients with VS(165).

2.3.6.2 Audiometry

Audiometry is used to assess a patient's degree of hearing function. Full testing includes assessment of middle ear function, hearing threshold and speech discrimination scoring.

Pure tone audiometry (PTA) scoring indicates the quietest sound detectable by the individual 50% of the time the stimulus is presented. It is performed using an audiometer, and both bone and air conduction is tested at frequencies ranging from 0.25 to 8 kHz. The intensity of the stimulus is recorded in decibels hearing level (dbHL). Results are then represented graphically; high frequency deterioration is often seen in aging. When summarizing left or right ear hearing threshold a pure tone average can be used, often this is average across frequencies 0.5, 1, 2, and 4 kHz(81).

Speech discrimination testing investigates the capacity of the patient to recognize and understand set of 25 words. The number of words that the patient can correctly repeat is presented as a percentage.

Gardner-Robertson scoring is used to combine PTA and speech discrimination score results (Table 2). Test results are scored are graded I to V scale, based on speech discrimination percentage and PTA results. A score of V indicates deafness, while a score of I indicates good hearing.

Table 2: Gardener-Robertson Hearing Scale

Grade	PTA (dB)	SD (%)
I: Good	0-30	70-100
II: Serviceable	31-50	50-69
III: Non-Serviceable	51-90	5-49
IV: Poor	90-100	1-4
V: Deaf	0	0
PTA = Pure tone average SD = Speech Discrimination Score		

Table 2 Gardener-Robertson scoring allows for objective evaluation of the degree of function hearing impairment suffered by the patient.

Multiple mechanisms underlie hearing loss, including blockage of the external air canals, middle ear effusions, cochlea damage and congenital disorders. Used in conjunction these tests can identify the type and degree of hearing loss present. Testing in VS normally consists of pure tone audiometry and speech discrimination scoring. The resultant scores are than tabulated to produce an overall hearing grade (Table 2).

In VS the most common presenting symptom is unilateral sensorineural hearing loss audiometry quantifies this. Rapid onset unilateral sensorineural hearing loss is a key red flag for the presence of vestibular schwannoma. Repeat audiometric testing can then be used to monitor for deterioration in hearing that may be an indicator for intervention.

Hearing thresholds have been shown to decline regardless of tumour growth rates, but may deteriorate faster in quickly growing tumours (53). Reports on the correlation between growth rate and audiometry test results have been conflicting, with some indicating there is correlation, and others not(166-169).

Hearing loss documented by audiometry is seen in almost all VS patients; characteristically this is a sensorineural hearing loss. Indeed unilateral hearing loss, with a mass lesion in the cerrebellopontine seen on MRI is the diagnostic hallmark of VS. It has been highlighted that tumours with lower growth rates had significantly higher rates of hearing preservation. Tumour size is also a predictive factor for postoperative hearing loss(170, 171).

2.3.6.3 Cognitive Testing

Cognitive function testing is not routinely undertaken tests in patients with VS or vestibular lesions. Regardless, physicians frequently note patients suffer from short-term memory loss, lack concentration and frequently have difficulty with multitasking(26). However, it must be noted that vestibular dysfunction does not result in general cognitive impairment. Animal studies utilizing single neuron recording have highlighted that both the cortex and hippocampus receive direct

vestibular input (29, 172). Animals with defined vestibular lesions show decreased capacity to perform tasks that require spatial memory, for example navigating water mazes (27). Studies of humans using PET scanning have also shown increased cortical and hippocampal activity following caloric stimulation of the vestibular system(28). In humans one study has shown that patients with bilateral vestibular lesions suffered a 16.9% decrease in hippocampus volume relative to controls(30). It has also been highlighted that humans with vestibular disorder display cognitive effects, with decreased capacity to complete tasks such as backward counting when compared to normal(173). The weight of evidence indicates that vestibular lesions can have cognitive impact. Given the significant links to the hippocampus this is likely to be in the form of spatial memory and spatial orientation. This fits with the clinically suggested short-term memory loss, and multitasking that requires switching between objects in space. These mechanisms could underlie some of the functional difficulties present following vestibular lesions. Better understanding of these mechanisms could lead to improved interventions and outcomes following vestibular lesions. Currently targeted cognitive testing is not clinically performed in monitoring vestibular patients and no studies could be found investigating cognitive deficit in those with long standing vestibular schwannoma.

2.3.6.4 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging with gandolinium enhancement is considered the clinical gold standard imaging technique for vestibular schwannoma(174). Computed tomography scanning is limited to diagnosis a 10 mm diameter lesion unless air contrast is used.

Following scanning tumours are classified as intracannalicular or extracannalicular and measured using a sub-millimetre digital ruler. Multiple quantification techniques exist for measuring tumour size. The American Academy of Otolaryngology Committee on Hearing and Equilibrium states that the diameter of the tumour should be measured parallel to the petrous ridge for extra cannalicular tumours(175). A second measurement can then be taken

perpendicular to this. Other proposed diameters include the anteroposterior, mediolateral and craniocaudal dimensions (176, 177). Intracannalicular tumours are quantified by measuring length along the internal auditory canal. Tumor volume can then be calculated using these measures. Full three-dimensional quantification can be performed by manual segmentation, circumference tracing, and computer automated grey shade differentiation (176, 178). Two-dimensional measures have shown to correlate relatively poorly with full three-dimensional measures(179). This is likely to due to the fact the calculations used to derive volume from diameter assume that the VS is spherical in nature, which is not always the case.

Overall there is good inter scanner reliability, allowing for comparison of MRIs from different centers (180). Luppino (178) et al suggested that there is a low degree of inter-observer reliability using a manual process, with intra-observer reliability dependent on examiners expertise and experience. Decreasing the slice thickness from 3mm to 1mm on MRI has shown to increase accuracy of tumour sizing (178).

Annual growth of 1.16mm of VS is held to be significant by the American Academy of Otolaryngology-Head and Neck Surgery(175). One study stated that the smallest detectable difference is 1.1mm linearly (181). However, this lies within the margin of measurement error, and therefore should not drive clinical decisions. This is particularly important for small tumors, where a small absolute increase in size can represent a significant proportional increase in volume.

Considered the gold standard for diagnosis of vestibular schwannoma, MRI scans allow for quantification of tumour size that informs management decisions. As well as this MRI scanning allows of monitoring of tumour growth. Tumour size at surgery is also a predictive factor for postoperative hearing loss(170, 171).

2.3.7 Localising Nerve of Origin

It has been suggested that a combination of vestibular tests may be used to localize the VS nerve of origin(182). The superior vestibular nerve carries fibres from the anterior canal, lateral canal and utricle, whereas fibres from the posterior canal and saccule run in the inferior vestibular nerve. Theoretically, tumours arising from one or other nerve would preferentially affect that nerves response and be reflected in the responses recorded in different tests. For example, a tumour arising from the superior vestibular nerve may be expected to reduce responses to Active-HIT, calorics, oVEMP or rotational chair testing, while the cVEMP remains normal. The converse would be expected for an inferior vestibular nerve schwannoma. Thus, cVEMP combined with either Active-HIT or calorics may allow identification of the tumour nerve of origin. This may aid selection of surgical approach when planning hearing preservation surgery.

No studies were found that used HIT or RCT to localize the nerve of origin. Chen et al found VEMPs useful to predict VS nerve of origin prior to surgery(183). A more recent study using VEMP and calorics have shown poor correlation between test results and nerve of origin(184).

2.4 Treatment Methods

2.4.1 Monitoring: the "Wait and Watch" Approach

Increased early identification of small tumours due to advancement in scanning techniques has led to an increase in the "wait and watch" approach in VS management. The increasing number of small tumours identified and questions surrounding the impact of intervention as well as tumour growth rates on quality of life has further popularized this method(74, 185).

Poor health, patient age, patient preference, small tumour size and lack of symptoms are the key selection criteria. Following adoption of this approach

patients undergo annual MRI scanning to monitor for tumour growth. It is argued that because VS are slow growing in nature this approach avoids unnecessary surgical morbidity(186, 187).

One case series found failure of treatment in 13.4% of cases, defined as where active intervention was required(188). In contrast to this treatment failure was seen in 74% of patients in a smaller study following with five years of follow up(189). Treatment failure was defined as necessary surgery. About one half to one third of conservatively managed patients develops hearing loss over three years regardless of tumour growth.

2.4.2 Radiotherapy in Vestibular Schwannoma

Radiotherapy as an alternative to microsurgery was first used in 1969(190). In the past forty years it has become an important method of treating small to medium sized VS. Stereotactic radiotherapy (SRT) was initially the recommended intervention (190). Recent studies, however, suggest that fractionated stereotactic radiotherapy (FRT) may result in better long term hearing preservation although this has not been fully validated(191). Higher resolution MRI and treatment planning software has allowed for better targeting of isodose centers(192).

SRT utilizes a stereotactic frame to immobilize the patient's head to allow for targeted dosing of the tumour. Dose targeting and quantification is then calculated from MRI scans. A single dose of around 14 GY ionizing radiation is administered with the goal of arresting tumour growth(193). Tumour growth is arrested 89.2%-96.8% of the time following SRT, with the volume doubling time decreasing from 1.36 years to 13.1 years(194). Hearing preservation rates have ranged from 58%-90%; a systematic literature review concluded hearing preservation is around 61% in doses of less than 13Gy and decreases to between 40% and 50.4% when doses of greater than 13 GY are used(195). Treatment failure including surgical intervention and continued growth rate has ranged from 2% to 13%(196, 197). The VII cranial nerve is intimately related to the VS

capsule and is particularly at risk from treatment. Rates of facial nerve dysfunction range from 0% to 5.2%. Patients undergoing SRT are said to lose 2.5 days of work following therapy(198). The lack of large comparative studies and RCTs mean that level one and two-evidence is lacking. Frequently smaller tumours, in which hearing preservation is possible, are selected for radiotherapy. This selection bias is likely to result in increased rates of hearing preservation post radiotherapy. Regardless, SRT shows good efficacy in treating small to medium sized tumours.

Fractionated stereotactic radiotherapy was initially used as a post surgical adjunct in VS. Recently several studies have demonstrated its usefulness as a stand-alone treatment measure(199-201). Fractionated stereotactic radiotherapy differs from SRT in that it utilizes several summative radiation doses to achieve the total desired dose. It is thought that doing so allows normal tissue to recover from the small dose it receives between sessions. This allows for much higher summative doses (Up to 2GY per session, 5 sessions per week, giving up to 60GY total dose). Fractioning in this manner also reduces tumor swelling sometimes seen post treatment. This is a concern in large tumors that already show mass effects (202).

Local control rates, defined as no tumor growth, have ranged between 86%-100%. Hearing preservation varies between 57% and 93% with auditory dysfunction seen in between 0%-4% of cases, and facial dysfunction between 0% and 4%(200, 201, 203). These results are comparable to those from SRT. In contrast, FRT requires a much greater time commitment from both the patient and oncology team than SRT.

2.4.3 Surgery in Vestibular Schwannoma

2.4.3.1 History

The first vestibular schwannoma was described following post mortem in 1777 (204). Not until 1810 were symptoms ascribed to this pathology, when facial

palsy, vestibulopathy, dysarthria, tinnitus and mass effects were described (205). However, it took until the end of the early 19th century, for the tumour to be localized based on patient symptoms. Charles Balance performed the first successful removal of vestibular schwannoma in 1894. Subsequently the suboccipital approach, now known as the retrosigmoidal approach, was described by Krause (206). The first translabyrinthine approach to was made in 1904(206). At this time problems associated with hemorrhage, dissection technique, equipment, and lack of imaging meant that mortality rates often exceeded 80%. As cautery, anesthesia, and blood replacement were introduced as well as the use of ventricular taps to lower CSF pressure mortality following total tumour removal began to fall. Bill House reinvented the translabyrinthine approach before the middle fossa approach was popularized. In the following years advancement of technology has lead to better pre, post and intraoperative management of VS patients. Preoperatively the advent of pantopaque x-ray contrast allowed for better localization of tumour(207). The subsequent development of CT and then MRI has allowed for better quantification of tumour size.

Furthermore the surgical microscope, diamond burs and irrigative suction allow for better access to and visualization of the surgical field. This coupled with intraoperative nerve activity recording has allowed for better identification and management of facial nerve function. Postoperatively improvements in surgical technique and technology have led to fewer postoperative complications. The cumulative advancements in vestibular surgery have led to a fall in mortality rates.

2.4.3.2 Translabyrinthine Approach

The translabyrinthine approach is frequently used in patients when there is little chance of retaining useful hearing. A hockey stick shaped incision is made two and a half centimetres posterior to the post auricular sulcus. The skin flap, underlying muscle and fascia is reflected and a mastoidectomy performed. Following identification of the facial nerve and lateral SCC a labyrinthectomy is

performed. The internal auditory canal is identified and the bone dissected away to allow access. At this stage important anatomical landmarks are again identified, and the facial nerve identified using a facial nerve stimulator. Subsequently, the tumour is debulked and dissected away from the facial nerve. Following this the posterior fossa dura is repaired and the wound is filled with fat, taken from the abdomen, and then sealed.

The translabyrinthine approach offers the most direct route to the cerrebellopontine angle and exposes the entire internal auditory canal(208). Furthermore little or no retraction the cerebellum is required, and the size of the tumour is not a limiting factor(209)

Several case series describe negative outcome rates as CSF leak 0.9%,
Meningitis 0.1%, Intracranial bleeding 0.8%, Non VII/VII nerve palsy 1.0%, Cerebellar Ataxia 0.7%, Death: 0.1% (210).

2.4.3.3 Retrosigmoid Approach

The retrosigmoid approach uses a vertical or slightly curved vertically orientated incision placed posterior to the sigmoid sinus. Subsequently, an occipital craniotomy is performed, and the dura and arachnoid mater opened. Because of the angle of approach, the cerebellum had to be retracted; corticosteroids, mannitol and hyperventilation were used to reduce retraction. Better instrumentation and CSF release from the basal cistern has meant that very little cerebellar retraction is required. Following retraction the tumour is identified and debulked. The seventh and eight cranial nerves are usually situated on the anterior surface of the tumour; therefore care must be taken not to inadvertently damage these during debulking, this is facilitated by identifying the nerves as they exit the brainstem and using the facial nerve stimulator to confirm that the facial nerve is not running more posterosuperiorly than expected.. Following tumour debulking the internal auditory canal can be accessed using a high-speed drill to remove bone over its posterior aspect , this allows identification of the facial and cochlear nerves so that the intracannalicular portion of the tumour

can be removed while preserving their integrity. From here the tumour is carefully dissected away. Following removal, the internal auditory canal is packed with soft tissue (fat and or muscle), the dura is closed and a cranioplasty is performed.

A case series by Samii et al (211)resulted in 0% mortality rate, 2% CSF leak, anatomical preservation of facial nerve in 98.5% of cases, and functional hearing preservation in 51%.

2.4.3.4 Middle Cranial fossa approach

An inverted 'U' incision is based and centered superior to the external auditory meatus allows exposure of the squamous temporal bone, and a middle fossa craniotomy is performed. The dura can then be elevated off the floor of the middle cranial fossa and temporal bone. Following this the internal auditory canal is 'skeletonised', and opened. Different surgeons utilize various landmarks used to identify the internal auditory canal. Subsequently the dura of the internal auditory canal is opened and reflected exposing the contents. The tumour is identified and the plane between the tumour and facial nerve clearly delineated. Similar to other approaches tumour removal begins with debulking, until enough space is present to carefully dissect the tumour away from the facial nerve. Following tumour removal the dura is replaced over the IAC, and mini-plates are used to replace the squamous temporal bone that was removed during the initial craniotomy and the wound is closed.

Arts et al (212) using the middle cranial fossa approach reported House Brackman facial nerve function of I/II in 96% of cases, and 62% of cases retaining rate of class A hearing . A case series by Gjuric M et al (213) resulted in a 0.4% mortality rate, CSF fistula in 2.2% of cases and meningitis in 1.2%. Improved outcomes were found with increasing surgical experience, with the last 254 cases resulting in no incidences of mortality, CSF fistula or meningitis.

2.5 Treatment Selection

Deciding on when and how to intervene is influenced by a variety of factors. The most commonly stated factors include tumour size, desire for hearing preservation, patient expectation and individual decision(214); with small tumour size and older age being common predictors of conservative treatment. Usually vestibular function and post surgical quality of life scores are not taken into account. The primary determinant of clinical outcome is tumor size at the time of intervention. Furthermore, traditional vestibular testing methods have shown little capacity to localize tumor origin, VEMPs have shown greater promise but more investigation is needed. The capacity to determine the nerve of origin may optimize the selection of the surgical approach, particularly for smaller tumors.

The primary potential clinical utility of vestibular testing in vestibular schwannoma lies in the capacity to quantify vestibular hypofunction, information that can be used to assist clinical decision-making; this is not current clinical practice. Assessing vestibular function prior to intervention may predict how much balance disturbance patients experience post-surgery, and the impact this may have on their return to full activites. If this is the case then pateints likely to experience severe vestibular dysfunction could receive early input from a physiotherapist with exerpeince in vestiblar dysfunction. Input could include vestibulo-ocular reflex strengthen exercise that may shorten the recovery time, resulting in a quicker return to full activities.

Access to these tests has been limited by both cost and their clinical limitations. Newer testing methods such as HIT with VOG are quicker, easier, more comfortable to administer, and give the opportunity to more readily integrate vestibular function testing into VS monitoring and management.

It has been shown that the discipline of the attending surgeon was a predictive factor for the choice of treatment(215). This may also influence the patient's

decision making. Comparing significant case series is difficult. Though each surgical approach is well established there is still inter-surgeon variation in techniques. While preoperative selection of patients likely to show good outcomes is likely to increase the success rates and minimize morbidity.

A 2012 systematic review concluded that middle cranial fossa approach is advantageous for hearing preservation in patients with small tumours(209). The translabyrinthine approach may be employed when there is no expectation of hearing preservation. While the retrosigmoid approach is appropriate for most tumours it also results in the highest rate of CSF leak.

Stereotactic radiotherapy has been shown to have better tumour control rate when compared to the watch and wait approach. This is a somewhat self-evident outcome as frequently patients who receive SRT are treated prior to tumour growth, or demonstration of lack thereof. In contrast patients who follow the watch and wait approach receive intervention following demonstrated tumour growth; with those not demonstrating growth not requiring SRT. This has both cost and health implications for the patient and society.

Current management protocols suggest the following management algorithm. Tumours and those below 20 mm intracranial diameter with no growth or, single observation, should follow conservative treatment. Tumours less than 20 millimeters with demonstrated growth should have radiotherapy or surgery. Tumours between 20-25mm on single scan should have radiotherapy or surgery and those greater than 25 mm on a single scan should have surgery(54).

Traditional vestibular testing methods have shown little capacity to localize tumour origin, VEMPs have shown greater promise but more investigation is needed. The capacity to determine the nerve of origin may optimize the selection of the surgical approach, particularly for smaller tumours.

Regardless, operative decision-making should be made on a case-by-case patient,

as this allows the informed decision-making, taking into account the full spectrum of functional tests as well as the patient's needs and wishes. Vestibular testing has the potential to play a greater role in decision making about VS intervention.

3. Methods

3.1 Study Design

A non-blind observational study was undertaken. Study endpoints were either one or two separate participant measures. These took place in March/April 2013 and September/October 2013. Testing took place in the Dunedin Hospital, Dunedin, Dunstan Hospital, Clyde and Southland Hospital, Invercargill. The primary purpose of the study was to validate a relatively new method of vestibular function testing, iral recording video HIT in comparison to calorics.

This study took place as a BMedSci (Hons) thesis project under the auspices of the Dunedin School of Medicine. Supervised by Dr. Nicholas Cutfield, consultant neurologist, A/Prof Patrick Dawes, ENT surgeon and A/Prof Cynthia Darlington, pharmacologist.

3.2 Ethics

The University of Otago Human Ethics Committee approved the study; reference code 12/303 (Appendix 9.1).

Maori consultation was also sought with the Ngai Tahu Research Consultation Committee (Appendix 9.2).

3.3 Recruitment

The study population was drawn from diagnosed vestibular schwannoma patients under the care of A/Prof Patrick Dawes. Consisting of New Zealanders living in the Southern District Health Board catchment, an initial sample size of 30 participants was targeted.

Participants were recruited by informal approach by post. Parcels contained a brief introductory letter and the University of Otago Ethics Committee approved information sheet (Appendix 9.3). Following this potential participants were contacted by telephone to assess interest. Questions and concerns were addressed at this time, potential participants were screened for exclusion criteria (Table 3), and verbal consent was obtained. If the participant consented to take part an examination time was arranged. A second call served to remind participants of the study two days before they were scheduled. Informed consent was then acquired prior to testing (Appendix 9.4).

Table 3 Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Any adult subject able to give informed consent diagnosed with unilateral vestibular schwannoma and who had not had this surgically removed.	• Any subject unable to give informed consent • Inability to lie still for 20 minutes. • Individuals in whom caloric and/or head impulse testing is contraindicated. • Severe structural neck problems • Severe narrowing of the spinal canal • Perforated Air drum • Congenital Nystagmus • Blindness • Bilateral vestibular schwannoma • Central pathology • Other vestibular pathology • Migraine • TIA • Multiple Sclerosis • Surgical Excision of Vestibular Schwannoma

Table 3 Legend: Inclusion and Exclusion Criteria: Exclusion criteria were selected to minimize the chance of bias or confounding factors in the data set while maximizing participant safety.

3.4 Participants

A total of **42** potential participants were contacted over the course of the study. **10** declined to participate. Their reasons included living out of Dunedin, other medical surgery planned, shifting hometown and anxiety about caloric testing (n=5). Of the **32** participants that agreed, data from **one** participant had to be excluded; this was due to the presence of congenital nystagmus. The remaining **31** met the inclusion criteria.

Vestibular function testing was performed in **31** participants that met the inclusion criteria with unilateral vestibular schwannoma, **13** of which were female. Subjects were used as their own controls, the unilateral nature of the vestibular schwannoma allowing for comparison between sides. Audiometry testing was only performed in **10** cases due to renovation of the Dunedin Hospital Audiology department. Repeat testing was performed in **10** subjects to show repeatability, mean age **63.9**, five of which were female. No participants had consumed alcohol within 24 hours of testing. No negative outcomes occurred throughout the testing, and no participant suffered an adverse event.

3.5 Testing Measures

3.5.1 Audiometry

The Audiology Department at the Dunedin Public Hospital performed the pure tone audiometry testing, following a standard protocol(216)**.** Testing was performed across frequencies 0.25 to 4 kHz. Thresholds were recorded in decibels hearing level (dBHL). A pure tone average was then calculated across 0.5, 1, 2, 4 kHz frequencies(81)**.** The Gardner-Robinson scoring criteria could not be calculated as resource limitations meant that speech audiometry testing was not performed.

3.5.2 Dizziness Handicap Inventory

Study participants completed the DHI(160)(Appendix 9.5). It was specified that dysfunction should only be in relation to dizziness and that the impact of other factors, such as hearing loss, should not be taken into account when answering the questionnaire.

3.5.3 Quantitative vHIT Testing

Quantitative HIT was performed in Dunedin, Clyde, and Invercargill. Participants were instructed to sit up right on a chair, with a fixed back support to avoid whole body rotation, approximately 1.5 meters from the fixation target to avoid fixation effects. Being close to the fixation target can increase gain as eye convergence increases the VOR(217). The same chair was used for each test. The patients then put on the EyeSeeCam goggles (Munich, Interacoustics)(Figure 6,7). These consist of a lightweight (60g) infrared camera, with integrated inertial sensor mounted on plastic goggles which record head movement and eye position signals at high frequency (200Hz). The camera's lightweight and firm scalp attachment mean slippage is minimized, a problem with older, heavier cameras. The camera is adjusted to fully identify the participant's pupil and the equipment measurements are calibrated as follows. The participant was instructed to sequentially fixate on 5 luminous dots projected by the EyeSeeCam at predefined angles of 8.5 degrees, with the central dot located on the fixation target, a four by four centimeter cross. A clustering algorithm detects these fixations, which are then localized within the software program. The parameters are then stored in Matlab and exported as a diagram. This is then checked manually to ensure appropriate fixation has taken place. If fixation was deemed to be inappropriate calibration was repeated.

Participants were then instructed to sit as still as possible while fixing vision on a target placed in front of them, keeping their eyes wide open and not blinking. It was explained that several movements of the head from side to side would be made. The need to not anticipate head movements and to relax their neck was

reinforced. The examiner than firmly placed their hands on the occiput and zygomatic bones, three practice impulses to each side were performed. Recording was then started and a minimum of 10 impulses to each side at velocities of 150 °/s or above were performed. These were performed in a pseudo-random order with a variable inter-test interval (0.5-4s) to avoid any anticipatory eye movements. Impulses were finished once an appropriate number had been performed, up to thirty to each side. The infrared camera recorded eye moment by tracking pupil location, while the inertial sensor quantified head movement. The eye position signal from the EyeSeeCam was then ported to matlab where it was differentiated to give an angular eye velocity (°/s). Simultaneously head acceleration was recorded and integrated giving an angular head velocity. This too was exported to matlab and presented in EyeSee software. Vestibular ocular reflex gain was calculated (at 60ms after onset of the impulse), the signals were then analysed as velocities. The VOR gain across multiple impulses was averaged to give a final figure. Where signal was impeded due to excess noise such as narrow palpebral fissure, long eyelashes, blinking, reflexive excessive pupil dilation or goggle slippage the head impulse testing is repeated until an accurate measure was generated. Sensitivity and specificity of HIT was calculated in comparison to caloric testing. This assumed a caloric canal paresis of 0.20 or greater is significant. Initially a HIT gain of < 0.74, was used. However, given the lack of literature on what is truly pathological in HIT testing, sensitivity and specificity was also calculated using more relaxed thresholds of significance, i.e. 0.92. This was to determine if currently accepted value, 0.74, lacked sensitivity in identifying vestibular dysfunction Gain asymmetry was also calculated in a manner analogous to Jongkees formula; $\frac{IpsilesionalGain \quad ContralesionalGain}{IpsilesionalGain + ContralesionalGain}$. Gain asymmetry of greater than 5.6% was held to be pathological. This values was based on one research paper by Schmid-Priscoveanu et al (123) as the use of gain asymmetry to evaluate VOR function has not been widely reported in the literature.

3.5.4 Caloric testing

Caloric testing was performed using the Aquastar 2.0 Irrigator Water (Difra, Welkenraedt) (Figure 8) following the Fitzgerald and Hallpike method(109). Participants were instructed to lie down on an examination bed with their head raised at 30 degrees to the horizontal to bring the lateral canal into the plane of irrigation. Participants were then advised that irrigations of cool to the contralesional and then ipsilesional, followed by warm to the contralesional and then ipsilesional would take place, highlighting the need to look straight ahead, with eyes wide open and not to blink. Calibration was analogous to that undertaken in vHIT. Opaque lenses were then inserted into the goggles placing the participants in the dark to avoid visual fixation, which will reduce nystagmus(218). Throughout testing participants were reminded not to blink, look straight ahead and to keep their eyes wide open. It was explained that the dizziness might last for up to two minutes, reach a peak then decrease. In order to ensure patient comfort cool irrigations were performed prior to warm irrigations. This was decided on clinical grounds as no clinically significant systematic bias in the induced caloric response can be related to order of testing(219). Irrigations were delivered at 30 °C ± 0.4 °C and 44 °C ± 0.4 °C via a decontaminated silicon irrigator nozzle(220). Irrigations lasted for 30 seconds and 250 ml ± 10 ml at 1.5 bar was delivered(221). Recording continued for three minutes after this, with a 7-minute interval between irrigations to avoid fatigue and summative effects. Good irrigations were confirmed via patient report of vestibular sensation of vertigo or vection, degree of wax dislodged during the irrigation, the angle of the waterspout back from the ear, and tympanic rubor. The 95% confidence limits for individual irrigations are typically 5 °/s and 57 °/s with the more marked nystagmus often seen following warm irrigation compared to cool(219). Patient alertness was maintained by simple conversation throughout the recording period(222). If significant doubts existed about the quality of the irrigation or the recording was a poor, i.e. insufficient mental alertness, inconsistent nystagmus, repeated blinking the suspect irrigation was repeated following the four standard irrigations. Nystagmus recordings were exported to matlab via EyeSeeCam and represented

graphically via ezeeye software (Munich, Interacoustics). The average peak slow phase velocity was taken from the ezeeye software graph. The canal paresis was then calculated according to Jongkees formula. A caloric canal paresis of 0.2 was considered to be pathological.

3.5.5 Cognitive Testing

Cognitive testing was performed using the CANTAB Cambridge cognition platform (223). The battery followed, Motor Screening Task, Big/Little Circle, Intra Extra Dimensional shift and Paired associates learning. Each test was administered using the standard script from the CANTAB eclipse 5 Test Administration Guide Version, Cambridge Cognition Ltd (2011) supplied with the CANTAB system to ensure the same instructions were given to each participant. Outcome measures including latency of response, number of errors, number of trials and stages completed were then compared to the reference normal groups taken from the literature to ascertain abnormal function(224).

3.5.6 Schwannoma Dimensions

All participants whose MRI scans of the cerrebellopontine angle were available were analyzed retrospectively for tumour size. All examinations were performed on 1.5 Tesla MR scanners (GE, Milwaukee) and with the measured scans consisting of T1 weighted gadolinium enhanced scan with slice thickness of 2-2.5mm. All patients underwent imaging following Southern District Health Board protocol for MRI.

Tumour size measurements were performed on 'Radiology measuring stations' following advice from a Consultant Radiologist. Measurements were performed using a submillimeter digital ruler. Measurements were taken at the largest observed schwannoma size in the axial and coronal planes. Blinded repeat measures were performed at later date to ensure intra observer reliability. Measurements were taken in the anteroposterior, transverse and longitudinal axes. This is consistent with measuring the greatest AP dimension in

extracannalicular schwannoma and longest dimension in the plane of the canal in intracannalicular, consistent with the published protocol(225). Tumors were then grouped according to size (Table 4).

Table 4 Schwannoma Classifications

Intrameatal	0mm
Small	1-10mm extrameatal
Medium	11-20mm
Moderately large	21-30mm
Large	31-40mm
Giant	>40mm

Table 4 Legend: Measurements are taken along anteroposterior dimension for extracannalicular tumours

Figure 6: EyeSeeCam and EzeEye Software

Figure 7: Mounted EyeSeeCam

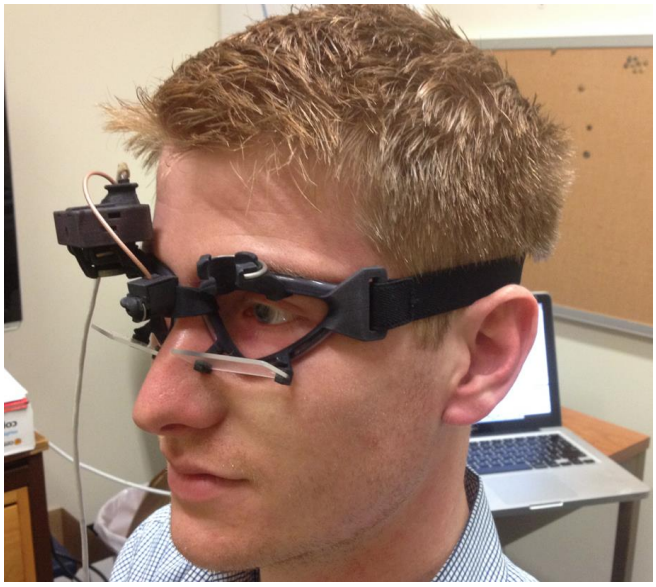

Figure 8: Aquastar Caloric Irrigator

3.6 Protocol

Participants were screened for exclusion criteria prior to testing. Following this non-excluded participants were then tested. ten participants underwent second testing to show repeatability. This was due to the study time frame, patient preference, as well as resource limitations. The rationale for the repeat testing was to ensure measurement repeatability and to confirm the stability of the vestibular dysfunction when cognitive testing was performed

3.6.1 Test One

Standard Examination Procedure:

1. Create new password protected participant data file
2. Informed Consent
3. Audiometry testing performed by the Audiology Department, Dunedin Hospital.
4. Dizziness Handicap Inventory questionnaire
5. Seat participant 1.5m from target
6. Mount goggles on the patient, align camera
7. Calibrate EyeSeeCam
8. 3 Head impulses to each side to accustomise participant to the procedure
9. A minimum of 10 Head Impulses was then performed to each side in pseudo-randomized order using roman number tables. Impulses were at a minimum of 150°/s
    a. EzeEye Software measured head velocity and eye velocity allowing for calculation of gain.
10. Break 10 minutes
11. Participants were then instructed to lie down on the examination bed, with the head angled at 30 degrees, for the caloric procedure
12. The EyeSeeCam was mounted on a pair of goggles, with opaque lenses to avoid visual fixation, and these were placed on the participant

13. With the lens was removed the EyeSeeCam was calibrated. The opaque lens was then replaced.
14. Calorics using the Fitzgerald and Hallpike technique were then performed with at least seven minutes break between each irrigation in order to avoid additive effects.
    a. Caloric information was recorded by EzeEye software using the EyeSeeCam. LC, RC, RW, LW, nystagmus was used to calculation canal paresis using the Jongkees formula
15. Thank participant

3.6.2 Test Two

Standard Examination Procedure:

1. Open participants pass word protected file
2. Cognitive function testing using CANTAB cognition battery
    a. Big Little Circle
    b. Motor Screening Test
    c. Paired Associated Learning
    d. Intra/Extra Dimensional Shift
3. DHI questionnaire
4. Seat participant 1.5m from target
5. Mount goggles on the patient, align camera
6. Calibrate EyeSeeCam
7. 3 Head impulses to each side to customize participant to the procedure
8. A minimum of 10 Head Impulses was then performed to each side in pseudo-randomized order using roman number tables. Impulses were at a minimum of 150°/s
    a. EzeEye Software measured head velocity and eye velocity allowing for calculation of gain.
9. Break 10 minutes
10. Participants were then instructed to lie down on the examination bed, with the head angled at 30 degrees for the caloric procedure

11. The EyeSeeCam was mounted on a pair of goggles with opaque lenses to avoid visual fixation, and these were placed on the participant
12. The lens was removed and EyeSeeCam was calibrated.
13. Calorics using the Fitzgerald and Hallpike technique were then performed with at least seven minutes break between each irrigation in order to avoid additive effects.
    a. Caloric information was recorded by EzeEye software using the EyeSeeCam. LC, RC, RW, LW, nystagmus was used to calculation canal paresis using the Jongkees formula
14. Thank participant

At the second testing audiometry was not performed due to resource limitations. Cognitive testing using the CANTAB battery was performed to evaluate cognitive function in the context of a stable vestibular lesion..

3.7 Outcome Measures

Primary outcome measures were gain on vHIT at a rotational velocity of above 150 degrees/second, and degree of canal paresis as a consequence of caloric stimulation. These measures were compared to determine sensitivity of vHIT versus the traditional clinical gold standard of caloric testing.

Secondary outcome measures included DHI score, audiometry, tumor size and cognitive measures. These were taken in order to elucidate the relationship between vestibular function tests, tumor size and patient impact.

3.7.1 Preliminary Data Inspection

Statistical analysis was performed in SPPS version 17 and $p<0.05$ was considered significant. Descriptive statistics were generated, including means and standard deviations, to scrutinize the data for overt anomalies and general trends. Following this Sharpiro-Wilk tests were performed to ascertain where

the data followed a normal distribution. It was held that where data had abnormal distribution central limit theorem would provide some protection against the violation of the assumption of normality (226, 227) Two-Tailed T-Tests were performed to compare for difference in bilateral measures, i.e. gain, and peak slow phase velocity, $p<0.05$ was considered significant. To consider that VS vestibular schwannoma results in a significant change in vestibular function $p<0.05$ was considered significant.

Exploratory factor analysis was performed to identify relationships between the data in a non-biased manner. Specific relationships were then probed using Pearson's correlation coefficients.

3.7.2 Secondary Data Analysis

Linear regression analysis was performed to identify the degree to which canal paresis could be predicted from other variables as well as further validating the correlational analysis. If two predictor variables have a correlation higher than 0.9 multicolinearality is indicated, this would call into question the validity of the multiple regression analysis. Sensitivity and specificity were calculated to evaluate the vHIT against the known calorics.

4. Results

4.1 Demographics

Thirty-two subjects with unilateral VS consented to participate. One subject was excluded, due to congenital nystagmus. The final number enrolled and included in the analysis was **31**, **13** women, mean age at testing was **62** years **(34 to 81 years)**. For **18** participants the tumours were right sided and for **13** tumours were left sided**.** Of the **31** participants **8** had undergone radiotherapy and **23** had followed 'wait and watch'.

Repeat testing 6 months after initial testing was possible and completed for **10** of the **30** participants **(n=10, 5 female**, mean age at repeat testing **63.9** years (**Range 51 to 81 years).** All of who were included in the statistical analysis.

No negative outcomes occurred throughout the testing, and no participant suffered an adverse event.

4.2 Vestibular Function

4.2.1 Calorics

Caloric testing was performed in all 31 participants (Figure 9); follow-up testing was performed in 10 participants. Shapiro-Wilk tests of normality on all caloric results showed that caloric canal paresis followed a non-normal distribution, **D (31) = 0.915, p = 0.020** (Table 5).

The mean canal paresis by Jongkees formula was **0.39 (SD = 0.30).** This asymmetry was reflected in peak slow phase nystagmus velocities achieved in both cool and warm irrigations, consistent with technically adequate irrigations and VOG recording: Cool 30°C

irrigations resulted in reduced response on the tumour side (**M= 5.74°/s, SD=4.71)** compared to the healthy side **(10.6°/s, SD=7.78), t (30)= -4.95, p <.001, r= 0.45;** warm 44°C irrigations resulted in a reduced response on the tumour side **(8.23°/s, SD=8.98)** compared to warm water irrigation on the non-tumour side **(17.54°/s, SD=11.68), t (30)= -5.34, p < .001, r=0.49.**

For the 10 participants who underwent repeat testing, the 6-month interval canal paresis was **0.41 (SD = 0.28).** Repeat canal paresis following the first testing **(0.39, SD=0. 21) was** not significantly different to Canal Paresis at the second testing, t test[1] **(0. 41, SD=0. 28), t (9)=0. 99, p=0. 35**

4.2.2 Head Impulse Test

Quantitative VOG head impulse testing was performed in all 31 participants (Figure 10).

The ipsilesional vHIT gain**, D (30) = 0.84, p < 0.001,** the contralesional vHIT gain**, D (30)=0.92, p = 0.033** and the gain asymmetry **D (30) = 0.86, p<=0.001,** were all significantly non-normal (Table 5).

At the first testing (n=31) mean gain (eye angular velocity divided by head angular velocity at 60ms after initiation of head movement) on the tumour side was **0.73 (SD= 0.31)**. Mean gain on the healthy side was **0.90 (SD=0.12**), which was different by t test[1] **(t (30) = -3.94, p<0.001, r=0. 34**.

Converting these to a mean gain asymmetry, by Jongkees formula, was **0.14 (SD = 0.27).**

Repeat HIT was performed in the 10 participants who underwent a second 6-month assessment. At the second measure mean gain on tumour side was **0.87 (SD = 0.25).** Mean gain on the contralateral non-lessoned side was **0.98 (SD=0.09).** Mean gain asymmetry was **0.04 (SD = 0.18).**

1. See methods page 64 for justification of using T-Test

In the sub group where repeat testing was performed, there was no significant difference between gain asymmetry following the first testing **(0.07, SD=0. 15)** than gain asymmetry at the second testing **(0. 04, SD=0. 18), t (9)=-0.926, p=0. 38).** This was also found for ipsilesional gain **t(9) = -0.661, p=0.525**

4.2.3 Sensitivity and Specificity of vHIT to Caloric Canal Paresis.

HIT sensitivity using a threshold of gain <0.74, sensitivity was 42%, specificity was 90%. When a gain threshold of <0.92 was used sensitivity was 80% and the specificity was 70%. HIT assessed by gain asymmetry had a sensitivity of 80% and a specificity of 70% (Table 6).

Figure 9: Caloric Irrigation Trace

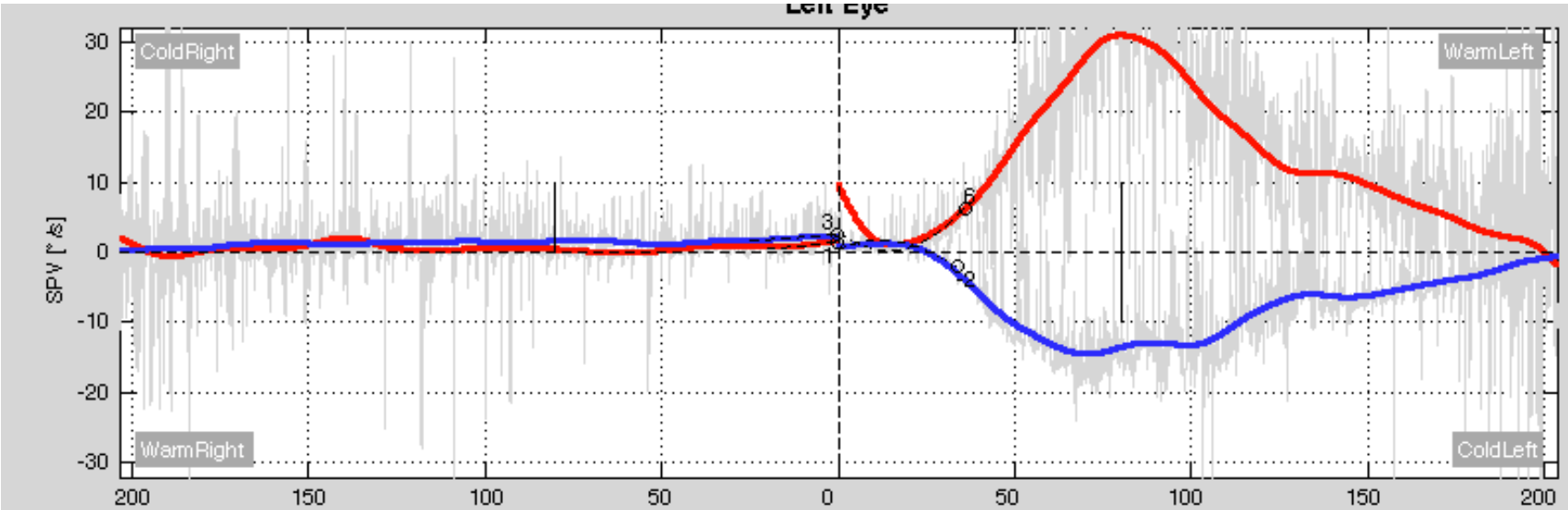

Figure 9 Table: The irrigation shows strong left sided response to caloric irrigation and almost no response to right sided irrigation indicating a high level of canal paresis.
Red: Warm Irrigation, Blue: Cool Irrigation

X Axis – Time in Seconds,
Y Axis Slow Phase Velocity in Degrees Per Second

Table 5: Tests of Normality

Shapiro Wilk	Statistic	df	Sig
Caloric Canal Paresis	0.91	30	0.02
Ipsilesional vHIT Gain	0.86	30	0.001
Contralesional vHIT Gain	0.92	30	0.033
Asymmetry of Gain	0.86	30	0.001
DHI	0.91	30	0.018

Table 5: Legend: The null-hypothesis states that the data comes from a normal population, significant result indicates that the null hypothesis is reject and the sample is not drawn from a normal distribution

Figure 10: Head Impulse Test Traces

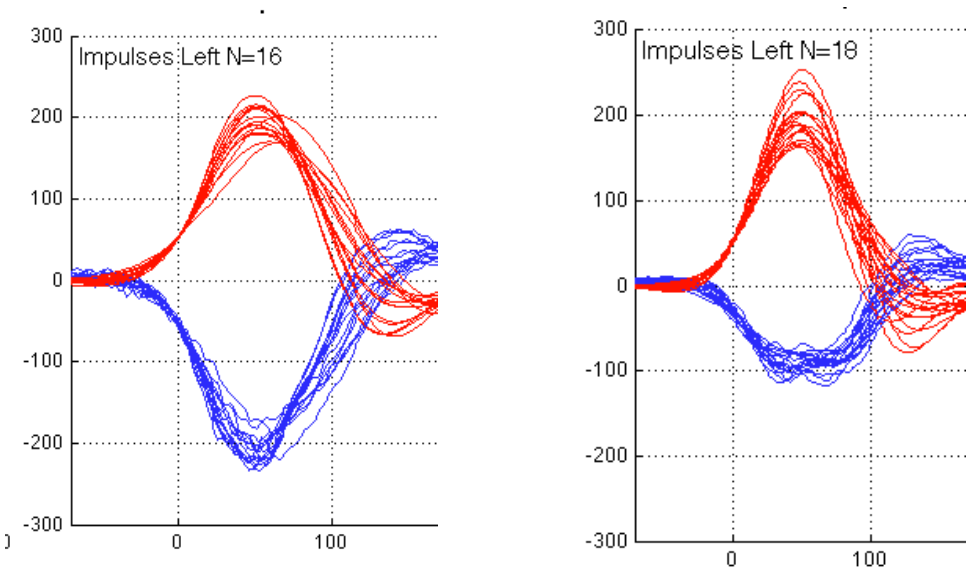

Figure 10 Legend: The left trace shows normal vestibular ocular reflex function. The right trace shows depressed vestibular ocular reflex function
Red: Head Movement , Blue Eye Movement

X-Axis: Time in MS
Y-Axis: Rotational Velocity in Degrees Per second

Table 6: Sensitivity and Specificity of Head Impulse Testing in Comparison to Calorics

Severity of Canal Paresis (Percentage)	**Number of Caloric tests**	**Positive head impulse test (<0.74)**	**Negative Head Impulse test (>0.74)**	**Positive head impulse test (<0.92)**	**Negative Head Impulse test (>0.92)**	**Pathological gain asymmetry (>5.6%)**	**Non Pathological Gain Asymmetry (<5.6%)**
0-25 %	10	1	9	3	7	3	7
25-50 %	10	1	9	7	3	7	3
50-75 %	6	3	3	5	1	5	1
75-100 %	5	5	0	5	0	5	0

Table 6 Legend: The total shows the number of positive and negative head impulse tests classified accordingly to severity of canal paresis

4.3 Tumour Size

Tumours were measured on radiology measuring stations using submillitmeter digitals rulers. Of the **31** tumours, **14** were intracannalicular and **17** were extracannalicular as determined by MRI observation, CT scans and participant notes. Three could not be measured, as due to administrative reasons the MRI scans were not available due to administrative reasons.

Of the extracannalicular tumours the measurements made in the cerebellopontine angle showed the mean transverse length was **12.69mm (SD=58.9)**, the mean anteroposterior was **8.53mm (SD=58.7),** and the mean longitudinal dimension **was 7.65mm (SD = 46.9).** Seven tumours were classified as small, seven medium, one moderately large and there were no large or giant tumours Three could not be classified as measurement could not be performed due to unavailable MRI scans.

For intracannalicular tumours the mean length along the internal auditory canal for intracannalicular tumours was **86.8mm (SD=28.0).**

4.4 Dizziness Handicap Inventory

Mean DHI score among participants was **19.30 (SD=17.34)** (Figure 11)**.** At follow up testing in 10 participants the mean DHI was **15 (SD=13.67)**

The mean DHI score at first testing **(14, SD=14.757)** was not significantly different from the scores from the same participants at follow up **(15, SD=13.6), t(9)=-0.6, p=.56**

Figure 11: Dizziness Handicap Inventory Distribution

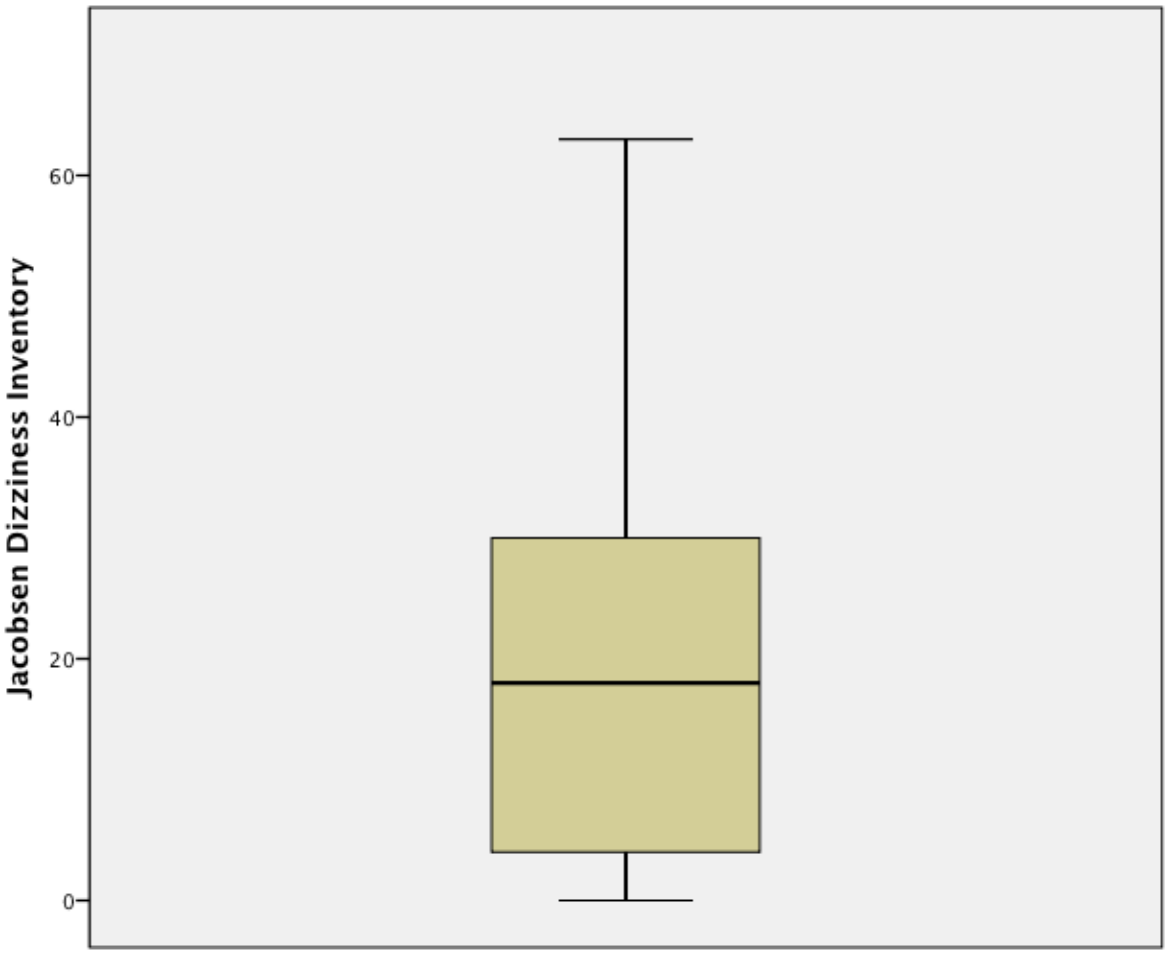

Figure 11 Legend The box shows interquartile range and the median score. Whiskers represent the minimum and maximum DHI scores

4.5 Audiometry

Pure tone audiometry was performed in **10** participants (Table 7). Mean pure tone average on the ipsilesional side was **70.5 (SD=29.8).** Mean pure tone on the contralesional side was 24.0 **(SD = 9.71).**

The PTA on the ipsilesional side **(M=70.5, SD=29.8)** was significantly greater than the average PTA on the contralesional side **(M=24.0, SD=9.71)**, **t(11)=5.107, p<.001, r=.07**

Table 7: Pure Tone Audiometry Thresholds At Standard Frequencies

	N	Minimum	Maximum	Mean	Std. Deviation
Non Tumour 0.5kHz	10	10.00	35.00	18.50	9.73
Non Tumour 1kHz	10	15.00	35.00	21.50	6.26
Non Tumour 2kHz	10	5.00	65.00	20.50	17.4
Non Tumour 4kHz	10	15.00	70.00	35.50	20.07
Tumour 0.5kHz	10	15.00	110.00	53.50	31.71
Tumour 1kHz	10	15.00	120.00	67.50	32.94
Tumour 2kHz	10	30.00	120.00	77.00	31.90
Tumour 4kHz	10	45.00	120.00	84.00	27.26

Table 7: Averaged Pure Tone Audiometry Frequencies

Table 8: Summary of Key Vestibular Function Measures					
	N	Minimum	Maximum	Mean	Std. Deviation
Caloric Canal Paresis, ratio 0-1	31	0.99	0.01	0.39	0.30
Ipsilesional vHIT Gain on; ratio 0-1	31	0.05	1.05	0.72	0.31
Contralesional vHIT gain; ratio 0-1	31	0.59	1.07	0.90	0.12
Gain Asymmetry ; ratio 0-1	31	0.84	0.47	0.14	0.27
Pure Tone Audiometry on Tumour Side (dbHL)	10	26.25	117.50	70.50	29.79
Pure Tone Audiometry on Non-Tumour Side (dbHL)	10	15.00	43.75	24.00	9.71
Dizziness Handicap Inventory (Score of 100)	31	0.00	63.00	19.30	17.34
Peak Slow Phase Velocity of Nystagmus following cool irrigation on tumour side °/s	31	0.00	16.65	5.74	4.71
Peak Slow Phase Velocity of Nystagmus following warm irrigation on tumour side, °/s	31	0.00	33.98	8.22	8.98
Peak Slow Phase Velocity of Nystagmus following cool irrigation on non tumour side, °/s	31	1.03	35.52	10.63	7.78
Peak Slow Phase Velocity of Nystagmus following warm irrigation on non tumour side, °/s	31	0.80	48.69	17.54	11.68

4.6 Comparative Statistical Analysis

4.6.1Factor Analysis

Exploratory Independent Factor Analysis was performed for ten items with orthogonal rotation (Promax) to elucidate relationships between the test variables. The Kaiser-Mayer-Olkin measure verified the sampling accuracy for the measure, KMO=0.75. Bartlett's test of sphericity (Chi Squared (28)=170.95, p <001), indicated that correlations between items were sufficiently large for factor analysis. An initial analysis was run to obtain eigen values for each component in the data. Two components had eigen values greater than one, and in combination explained 75.6% of the variance. Given the sample size and the scree plot convergence 2 components were retained in the final analysis as they accounted for the majority of the variance (Table 9). The items that cluster on component 1 suggest component 1 represents the degree of vestibular impairment. Items that cluster on component 2 suggest that it represents a degree of functional impairment, i.e. DHI.

Significant loading was seen in between tumour dimensions and the vestibular function measures of both caloric testing and HIT.

4.6.2 Pairwise Correlations

Items that showed significantly clustering on a single factor were further investigated with pairwise correlations using Pearson's correlation coefficient (Table 10). Significant results were found for Canal Paresis/ Ipsilesional Gain with each other and tumour size.

Table 9: Factor Analysis Component Matrix:

	Component	
	1	2
Transverse Dimension	-0.89	0.07
Longitudinal Dimension	-0.87	0.23
Ipsilesional vHIT Gain	0.85	0.30
Caloric Canal Paresis	0.83	0.02
Asymmetry of Gain	0.82	0.12
Anteroposterior Dimension	-0.77	0.37
Contralesional vHIT gain	0.77	0.44
Dizziness Handicap Inventory	-0.18	0.84

Independent Factor Analysis

Table 9 Legend: Degree of component loading indicates the closeness in the relationship between the two variables

Table 10: Pearson's Pairwise Correlations

Correlated Pair	r-score	Significance level p(two-tailed)
Ipsilesional Gain vs Canal Paresis	r=-0.83	p<0.001
Canal Paresis vs Audiometry	r=-0.12	P=0.072
Ipsilesional vHIT Gain vs Audiometry	r=-0.30	p=0.35
Ipsilesional vHIT Gain vs Tumour Size	r=-0.62, r=-0.47 r=-0.57	p<0.001 p<0.001 p<0.001
Canal Paresis vs Tumour Size	r=0.57 r=0.58 r=0.58	p=0.001 p=0.007 p=0.001

Table 10 Legend: Pearson's Correlation Coefficients. Strength of correlation is graded between 0-1, with one indicating perfect positive correlation.

4.7 Modeling Canal Paresis

No variables showed a Pearson correlation coefficient above 0.9. This indicates there is no multicollinearity, and therefore multiple regressions are a valid comparative statistical methodology.

Multiple regression analysis was used to test how well the vestibular battery, including HIT and DHI, predicted canal Paresis. Results indicated that creating a model for canal paresis utilizing other measures of vestibular function explained 73.9% of the variance **(R=0. 894, F (6,26)=13.274, p<. 001) (**Table 11,12). It was found that ipsilesional vHIT gain predicted canal paresis **(β=0. 721, p<. 001)** , as did the DHI **(β=-0.261, p=. 027)**(Table13)**.**

Table 11: Multiple Regression Analysis Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	0.894[a]	0.8	.74	6.16

a. Predictors: (Constant), Longitudinal Dimension, Dizziness Handicap Inventory, Contralesional vHIT gain , Ipselesional vHIT Gain, Transverse Dimension, Anteroposterior Dimension

Table 11 Legend Adjusted R Square value indicates modeling canal paresis using alternative vestibular battery measures accounts for .739 of the variance.

Table 12: Multiple Regression Analysis ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1.97	6	0.33	13.27	0.000[b]
	Residual	0.493	20	0.025		
	Total	2.46	26			

a. Dependent Variable: Caloric Canal Paresis

b. Predictors: (Constant), Longitudinal Dimension, Jacobsen Dizziness Inventory, Contralesional vHIT gain, Ipsilesional vHIT Gain, Transverse Dimension, Anteroposterior Dimension

Table 12 Legend: ANOVA testing the variation showed in the model is significant

Table 13: Multiple Regression Analysis Coefficients

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-1.07	0.39		-2.75	0.012
	Ipsilesional vHIT Gain	0.70	0.17	0.72	4.20	0.000
	Contralesional vHIT gain	0.30	0.46	0.12	0.66	0.52
	Dizziness Handicap Inventory	-0.005	0.002	-0.26	-2.36	0.03
	Transverse Dimension	0.007	0.011	0.13	0.59	0.56
	Anteroposterior Dimension	-0.002	0.012	-0.04	-0.17	0.87
	Logtitudinal Dimension	-0.009	0.02	-0.14	-0.47	0.65

a. Dependent Variable: Caloric Canal Paresis

Table 13 Legend: Model indicates ipsilesional vHIT gain and DHI are significant predictors of canal paresis. With ipsilesional vHIT gain accounting for the majority of the variance.

4.8 Modeling Canal Paresis using vHIT Gain

Linear regression analysis was performed on a subset of the data to investigate the robustness of the model. Specifically, this was used to see if ipsilesional vHIT gain was predictive of canal paresis. A good predictive model would indicate that there is a strong relationship between the ipsilesional gain, PTA test results and the participants' canal paresis.

Results showed that 68% of the variance could be explained (**$R=0.831$, $F(7,9)=64.67$, $p<0.001$ (**Table 14,15). It was found that ipsilesional vHIT gain significantly predicated canal paresis **($\beta=0.831$, $p<0.001$)**(Table 16)

Table 14: Linear Regression Analysis Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	0.83[a]	0.69	0.68	0.168

a. Predictors: (Constant), Ipsilesional vHIT Gain

Table 14: Legend: Adjusted R Square indicates modeling canal paresis using HIT gain accounts for 0.68 of the variance

Table 15: Linear Regression Analysis ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1.82	1	1.819	64.69	0.000[b]
	Residual	0.82	29	0.028		
	Total	2.64	30			

a. Dependent Variable: Caloric Canal Paresis

b. Predictors: (Constant), Ipsilesional vHIT Gain

Table 15 Legend: ANOVA testing the variation showed in the model is significant

Table 16: Linear Regression Analysis Coefficients

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	Collinearity Statistics	
		B	Std. Error	Beta			Tolerance	VIF
1	(Constant)	-0.98	0.079		-12.42	0.000		
	Ipsilesional Gain	0.804	0.10	0.831	8.04	0.000	1.000	1.000

a. Dependent Variable: Caloric Canal Paresis

Table 16 Legend: The model indicates that Ipsilesional gain accounts for 0.831 of the variance found in the model.

4.9 Cognitive Function

Cognitive Function was assessed in ten participants (Table 17). Mean Intra-extradimensional shift adjusted error in the vestibular schwannoma group **(M=21.6, SD=17.81)** was significantly more than mean Intra-extradimensional shift adjusted error in normals from the published literature **(M=4.40 SD=6.13), t(59)=5.55,p=.001.**

Mean paired associates learning Total Error Adjusted in the vestibular schwannoma group **(M=32.4, SD=36.03)** was significantly more than the mean paired associates learning total error adjusted in normals from the published literature **(M=19.58, SD=14.33), t(59)=3.40, p=0.001**

Further multiple regression analysis was performed on the participant's cognitive percentiles to investigate the robustness of the model. Multiple analyses revealed no significant effects. However, specifically looking to see if canal paresis could be predicted from Intra extra dimensional shift. Regression analysis found **77.5%** of the variance could be explained **(R=0.92, F(5,2)=13.03, p=.01** (Table 18,19) **.** It was found that Intra-extra dimensional shift–total error significantly predicted canal paresis **(β=-0.73, p=.039)** (Table 20)

Table 17: CANTAB Cognitive Measures Summary

Test Performed	N	Minimum	Maximum	Mean	Std. Deviation
Big Little Circle Percent Correct	10	97.50	100.00	99.50	1.05
Intra-Extradimensional Shift Total Error	10	9.00	59.00	21.60	17.81
Intra-Extradimensional Shift Stages Complete	10	7.00	9.00	8.80	0.63
Motor Screening Task Mean Latency, ms	10	709.3	1396.00	949.86	244.43
Motor Screening Task Mean Error	10	6.61	26.10	10.85	5.62
Paired Associates Learning Total Error Adjusted	10	3.00	115.0	32.40	36.03
Paired Associates Learning Total Errors 6 shapes adjusted	10	0.00	45.00	12.60	14.14
Valid N (listwise)	10				

Table 17 Legend: CANTAB Test Results Included both total number of errors and stages complete

Table 18: Cognitive Linear Regression Analysis Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Durbin-Watson
1	0.92	0.839	0.78	0.11	1.96

Table 18 Legend: Modeling canal paresis using Intra-Extradimensional Shift total error accounts for 0.459 of the variance

Table 19: Cognitive Linear Regression Analysis ANOVA

Model	Sum of Squares	df	Mean Square	F	Sig.
Regression	0.328	2	0.164	13.03	0.010
Residual	0.063	5	0.013		
Total	0.390	7			

Table 19 Legend: ANOVA testing the variation showed in the model is significant

Table 20: Cognitive Linear Regression Analysis Coefficients

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	Collinearity Statistics	
		B	Std. Error	Beta			Tolerance	VIF
1	(Constant)	0.011	0.16		0.066	0.95		
	Intra-Extra Dimensional Shift Total Errors	-0.008	0.003	-0.73	-2.63	0.039	1.000	1.000
	(Constant)	-. -		-				

Table 20 Legend: The model indicates that Intra-Extradimensional Shift total error accounts for 73% of the variance found in the model

4.10 Summary of Key Results

1. Subjects who declined to participate in this study most commonly volunteered apprehension regarding caloric irrigations, potentially supporting the rationale of this study.
2. Exploratory independent component analysis shows caloric canal paresis, vHIT gain, and tumour sizes all clustered on the same factor
3. Video-HIT ipsilesional gain correlates with degree of canal paresis
4. A valid linear regression model uses HIT ipsilesional gain to predict caloric canal paresis.
5. Setting a threshold of vHIT gain to <0.92 gave a sensitivity of 80% for vHIT in comparison to caloric testing (25% canal paresis threshold for abnormal).
6. Symptom score, the DHI did not correlate with vestibular reflex function, as is the case in other vestibular disorders.
7. Repeat testing of 10 subjects revealed stable vestibular function over six months. Specific cognitive domains in the CANTAB Cognitive battery were abnormal in this group.

5. Discussion

Caloric testing has formed the backbone of quantitative vestibular analysis for over a hundred years. Though effective in identifying vestibular hypo function, it has been likened to testing hearing with thunder, and vision with lightning. Caloric testing can also induce a significant level of patient discomfort. While the equipment required means that testing is often restricted to specialized vestibular centers. More widespread use of vestibular function testing could result in better diagnosis and management of vestibular dysfunction. Unfortunately, newer testing modalities have consistently failed to reach comparable levels of accuracy. Validation of a new quicker testing method with less patient discomfort could lead to widespread adoption of quantitative vestibular testing. A consequence of better quantification of vestibular dysfunction, being improved management of the patients overall condition.

The study contained in this thesis tested the hypothesis that head impulse testing using video oculography is comparable to caloric testing as a measure of vestibular function in patients with unilateral vestibular schwannoma. Head impulse testing with video-oculography has been shown in one study to have comparable levels of accuracy to caloric testing(132). The testing process has few exclusion criteria, and causes less discomfort than calorics. It also assesses vestibular capacity in the normal range of function. Validation of this methodology could lead to wider testing of vestibular function and better management of patients.

5.1 Participant Demographics

Mean age was 62 years, this is similar to the one New Zealand case series of 97 vestibular schwannoma patients, with an average age of 54 years, the male to female ratio is also similar(228). Both studies are comparable to a systematic review highlighting the mean patient age 62 (range 52-75) years, with comparative gender splits(74). These results suggest a degree of external

validity, indicating that comparisons between similar studies can be made. While differences between this and other studies are unlikely to be due to age related effects.

It is interesting to note that of those that declined to participate, five did so due to volunteered apprehension about tolerating caloric testing. In contrast no participants volunteered apprehension about undergoing vHIT. This indicates that caloric testing is perceived as a distressing experience, underlying the importance of this study in validating alternative methods of vestibular function testing.

5.2 Sensitivity and Specificity of Head Impulse testing

Both vHIT gain using a cut off of 0.94 and gain asymmetry calculated by comparing the difference between left and right-sided gain, similar to the Jongkees formula show more promise than simple analysis of gain values if the gain is set at 0.74. There is limited data on normal gain values. The use of 0.74 was based on a publication that reported gain two standard deviations (SD) below the mean as the lower cut off for normal(123). Given the size of this study, using this value as the cut-off for abnormal gain is somewhat questionable. The authors analysis assumes that the data is normally distributed. For sample sizes smaller than 30 (n=24), this assumption may not be true. Further highlighting this point the Shapiro-Wilk test of normality on the gain data (n=31) reported in this thesis found it did not follow a normal distribution. Given it is likely that gain values are not normally distributed assuming normal gains fall within 2 SD of the mean may not accurately represent normal gain values.

To increase the sensitivity of the vHIT a lower threshold of 0.92 was also considered. Given the lower threshold it is likely that increased vestibular dysfunction will be identified, if the corresponding specificity is still high however this may be acceptable. The use of gain asymmetry to identify vestibular function is a novel with only one of the few studies exploring gain asymmetry considering asymmetry greater than 5.6% as pathological. Given this method is more analgous to l Jongkees formula for assessing caloric asymmetry, it is surprising that its use has not found greater scope. To further investigate this a gain assymetry value of 5.6% was utilized in this study when considering pathological gain asymmetry (123), this was then compared to raw gain, the value more commonly used. In comparison to caloric, vHIT shows a sensitivity of 42%, and a specificity of 90%, using an asymmetry cut off of 0.74, higher than published results using HIT without video oculography(111, 128). However, when a gain value of <0.92 is taken to be pathological the sensitivity increase to 80% while the specificity decreases to 70%. The same sensitivity and specificity is found by using gain asymmetry to assess pathology. Using a gain value of 0.92 as the cut off sensitivity is comparable to oVEMP, which shows sensitivity ranging between 61.5%-80% and much lower specificity at 50%(148, 152, 156, 159). It is also more consistently superior to cVEMP, which shows a sensitivity ranging between 37.5%-69%(148, 152, 156).

The increase in sensitivity when comparing canal paresis and vHIT gain asymmetry is likely due to the nature of the measures. With calorics absolute slow phase nystagmus values are used to measure vestibular function; due to their wide normal range, between 5-67 °/s, the slow phase values from all four irrigations are then converted into a canal paresis ratio. Though more restricted, it is possible that HIT gain follows this same pattern, with a normal gain ranging between 0.74-0.96. Vestibular ocular reflex gain asymmetry therefore provides a more analogous comparison to canal paresis, where it is the response difference between the sides that is held to be clinically significant.

Alternatively the increased sensitivity found by decreasing the cut off for abnormal gain to 0.92 may be due to up-regulation of the cervico-ocular reflex necessitating this less strict criterion. Cervico-ocular responses are greatly

increased in both individuals and primates with diminished vestibular ocular response(24, 229-231). It is possible that HIT activates the cervico–ocular reflex via neck proprioceptors. This could then result a compensatory increase in gain, particularly in vestibular compensated individuals. Other visual gaze stabilization pathways, such as smooth pursuit, are unlikely to impact on HIT recording given they operate at much lower frequencies. If this were the case a lower cut off for pathological gain (i.e. 0.92) would result in greater sensitivity of testing, as in found in the results of this thesis.

Both vHIT gain and vHIT gain asymmetry mirrored calorics canal paresis. Gain towards the side of lesion showed a strong, statistically significant negative correlation with canal paresis, i.e. as gain deceases canal paresis increases. This effect remained when canal paresis was correlated with gain asymmetry, though the relationship was weaker. Further testing using multiple regressions using vestibular measures to model canal paresis showed a highly significant model accounting for 74% of the variance. Of the predictive factors, only two were significant, ipsilesional vHIT gain and DHI. However any change to vHIT was mirrored very closely by changes in canal paresis, as vHIT accounted for the majority of the variance. A single regression analysis, modeling gain asymmetry was again highly significant with vHIT accounting for the majority of the variance in calorics. The differences between the statistical models are likely to have arisen from the nature of the tests themselves. Caloric testing stimulates vestibular response through convection currents, volume displacement and direct temperature effects. This is equivalent to a rotational frequency between 0.002-0.005 Hz. With vHIT examiner driven head rotation to one side induces endolymph movement, which deforms the cupulae of both lateral semicircular canals. This induces both a contralateral inhibitory and an ipsilateral excitatory response along the vestibular nerve to the vestibular nuclei. In patients with a unilateral deficit, the diminished response from the ipsilesional side and saturation of the contralesional inhibitory response leads to a failure of the VOR and a catch-up saccade. This occurs at frequencies of between 4 to 6 Hz and is therefore more representative of day-to-day head movement. It should be recognized that each test is stimulating the vestibular system at a different

frequency; consequently it is possible that the difference between the two measures is due to underlying differences in the afferent conduction pathways or how these responses are interpreted in the vestibular nuclei. Alternately a combination of both may play a role. No literature could be found detailing how different stimulation frequencies effect the processing of vestibular input. Regardless of this difference the degree to which gain and gain asymmetry mirrored variance in canal paresis implies that they are appropriate analogues.

It is also worth considering that vestibular function is known to deteriorate with age, deterioration affects both right and left sides similarly(232). Therefore, a unilateral measure of vestibular function could give the impression of a one sided vestibular deficit if significant age related deterioration has occurred (i.e. a false positive result). However, by comparing sides, which are likely to have experienced equal deterioration, one removes this problem.

Both calorics and vHIT assess the VOR primarily by stimulating the lateral semicircular canal; which is innervated by the superior division of the vestibulocochlear nerve . Initially it was believed that most VS arise from the superior aspect of the vestibulocochlear nerve(233), more recently it has been suggested that this is not so(234). With several authors reporting a much higher frequency of inferior VS to superior VS (235-237). Under reporting of inferior VS may because they cannot be classified as readily(236). Therefore if the VS is impinging on the inferior vestibular nerve function and reducing its function, but not superior nerve function then both vHIT and calorics testing may fail to accurately assess vestibular function. This would provide some explanation as to why both tests did not produce abnormal responses for all VS. It is therefore advisable when monitoring vestibular function in VS that a measure of the inferior vestibular nerve function, i.e. cVEMP, be used.

The relatively high sensitivity of head impulse testing using a cut off of 0.92 and gain asymmetry as well as the degree to which a change in vHIT results are mirrored by a change in canal paresis indicates that video head impulse testing using video oculography is a promising alternative to caloric testing, though further research is needed.

5.3 Audiometry

Audiometry results showed significant hearing impairment on the side of the tumour. This is consistent with the well-established body of literature highlighting hearing loss in 95% of patients with VS (238). It is worth noting that only 10 pure tone audiometry tests and no speech discrimination scores could be assessed due to resource limitations. Pure tone audiometry showed a positive correlation with anteroposterior tumour and vertical tumour dimension. However, it showed no correlation with DHI or other vestibular function measures. The correlation of audiometry and tumour size could suggest that the dysfunction is due to tumour mass effects, either physical interruption of the blood supply or of the nerve conduction pathway. This is consistent with the mechanism of injury highlighted in the literature, given that this is the same proposed mechanism for vestibular dysfunction it is interesting that they did not correlate(22, 187). The difference may be due to vestibular compensation without hearing compensation. Perhaps highlighting that the auditory fibers of the vestibulocochlear nerve are more sensitive to schwannoma growth.

Furthermore tumour size is a known predictive factor for postoperative hearing loss(239, 240). Given that hearing will deteriorate regardless of tumour growth, degree of hearing preservation is a key consideration when selecting the wait and watch approach over surgery. Consequently hearing preservation must be taken into account in patient management.

5.4 Dizziness Handicap Inventory

The degree to which balance dysfunction can result in health related morbidity means that the impact of VS on balance is important. Indeed given the impact of balance function on quality of life it is surprising that it is not frequently measured in VS more often. The DHI scores were comparable with results published in the literature, indicating that there is a consistent level of

dysfunction with VS(163, 164). No vestibular or hearing function parameter was found to correlate with the DHI score. This is likely due to the capacity of the vestibular system to functionally compensate. Vestibular schwannoma is a slow growing, sometimes-stable unilateral vestibular lesion; this allows the vestibular system to compensate over time. While the up regulation of the visual and other systems may also play a contributing role(44, 241). It is possible that in the context of a rapidly growing VS the balance system would not be able to compensate and a greater degree of vestibular dysfunction would be realized. If this were the case serial DHI assessment could be used to monitor for tumour growth; with significant increase in DHI score an indicator for failure of conservative treatment and earlier MRI scanning.

5.5 Tumour size

Tumour size is an important factor in presurgical decision-making, given that tumour size at surgery is predictive of postoperative hearing loss, and facial nerve function(170, 171). In this study VS sizes were consistent with the published literature(76, 77). Tumour size showed a strong positive correlation with vestibular function measures, this is consistent with the proposed mechanisms of dysfunction and the published literature; while highlighting that though functional compensation may occur both gain and canal paresis do not return to pre lesion levels (22). Perhaps the most useful measure is rate of tumour growth. Relating tumour growth to changing vestibular function measures could allow for better presurgical decision making. Such as using vestibular testing to predict patients who are likely to have more post-op vertigo and who will benefit most from postoperative vestibular rehabilitation. Unfortunately this could not be performed due to the short time frame of the study.

5.6 Cognitive Testing

The CANTAB results indicated that VS impacts upon cognitive function to some degree. Cognitive testing indicated participants were in the lower percentiles of function. Which was particularly marked for Intra-Extra Dimensional shift. This is consistent with linear regression model that indicated that Intra-Extra Dimensional Shift results are a significant predictive factor for caloric canal paresis. The significantly higher number of errors in Paired Associates Learning and Intra-Extra Dimensional Shift seen among the participants are consistent with the literature highlighting the vestibular basis for some cognitive deficits. These underlying cognitive deficits may explain some of the associated psychiatric issues seen in patients with vestibular lesions(242, 243). Better assessment of this aspect of vestibular dysfunction could lead to more effective interventions and better patient outcomes. These results while highlighting that cognitive testing may have a role to play in vestibular function testing and treatment, suggest that further study with a larger sample size is indicated.

6. Limitations and Further Work

One source of concern throughout this study was a acquiring a large enough sample to have sufficient power to be able to draw valid conclusions. Throughout the study attention was paid to this by contacting those living the greater Otago Southland area and not limiting recruitment to those in the Dunedin metropolitan area. Regardless, conclusions drawn here about repeated measures have to be interpreted cautiously due to the small sample size. This was largely due to the time frame limitations imposed by the short duration of the research period (1year). Audiometry testing was poor, both in terms of final numbers and breadth of testing modalities

Further work is needed following up the remainder of the cohort, to show the repeatability of the data collected and allow a fuller picture of cognitive function.

This thesis examined only two measures of vestibular function, calorics and vHIT, but excluded other methods such as VEMPs. Vestibular evoked myogenic potentials are an increasingly relevant method of investigation vestibular function. Inclusion in this study would not only have allowed investigating the relative sensitivities of each method but how they work in conjunction with one another. Considering the anatomical arrangement of the vestibular nerve it is perhaps the use of these different testing methodologies in conjunction with one another that would be most useful. A long-term prospective cohort study with serial MRI scanning could then relate degree of tumour growth to vestibular function test results and recurrent DHI assessment. This would allow for the development of a standardized vestibular testing battery. To validate this further observational studies investigating the range of normal HIT gains in the general population are needed, as well as further longitudinal observational of clinical cohorts such as this.

Other possible measures of vestibular function available when performing vHIT include observation of catch-up saccades (overt and covert) and 3D vector analysis. A 3D analysis of rotational eye movements was not performed due to lack of expertise. This would have ensured rotation was only in the horizontal plane activating only the horizontal semicircular canals. Observation of saccades is the traditional measure a positive head impulse test. As the goal of the study was to identify quantifiable measures of gain values this analysis was not performed. However, frequency of covert saccades would have added to the research by highlighting the lack of sensitivity of qualitative head impulse testing. This would further justify the use of video-oculographic equipment.

The use of the participants as their own controls limited the degree to which the cognitive data could be interpreted. Reliance on already published data means that there is poor matching between subjects and controls. This increases the likelihood of confounding and spurious results. Indeed in this study it is possible that the marked difference seen in the Intra-Extra Dimensional shift and Paired Associates Learning errors is due to age related confounding, given that there

was a large age difference between the group tested and the normal values comparison taken from the literature and used for. More definitive studies on vestibular cognition and its relationship with vestibular function measures and functional outcomes are needed. With a larger sample size and properly matched control group being the key factors.

7. Conclusion

Video HIT is a promising alternative to caloric testing for measuring vestibular function in VS as it shows good correlation with, and sensitivity to, the standard caloric testing as seen in this cohort. With qualitative feedback indicating it is a more acceptable test. Further study is needed to validate the selection of 0.92 as the cut off for abnormal gain.

Given that vHIT operates at a frequency range that is closer to everyday function it may better reflect vestibular disturbance than calorics, however this has not been shown in this, or other studies. Further prospective observation is required to determine if changes in HIT reflect changes in tumour growth, and if this may be as an important factor when considering outcome following either surgery of radiotherapy.

Although hearing function deteriorates regardless of proven tumor growth, audiometric monitoring is an important part of current management additional to MRI.

Vestibular function is similarly important yet is relatively neglected in the clinical setting. The availability and degree of validation of a relatively new testing modality demonstrated in this thesis, provides an indication that vestibular monitoring may have a role to play in the 'wait and watch' presurgical management of VS.

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9. Appendices

9.1 Ethical Approval

12/303

Academic Services
Manager, Academic Committees, Mr Gary Witte

23 November 2012

Dr N Cutfield
Medicine
Dept. of Medical and Surgical Sciences
Dunedin School of Medicine

Dear Dr Cutfield,

I am writing to let you know that, at its recent meeting, the Ethics Committee considered your proposal entitled "**Vestibular Function in Acoustic Neuroma**".

As a result of that consideration, the current status of your proposal is:- **Approved**

For your future reference, the Ethics Committee's reference code for this project is:- **12/303**.

The comments and views expressed by the Ethics Committee concerning your proposal are as follows:-

While approving the application, the Committee would be grateful if you would respond to the following:

Please ensure the following statement on contacting the Human Ethics Committee is included at the end of your Information Sheet:

"This study has been approved by the University of Otago Human Ethics Committee. If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479 8256). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome."

The Committee would be grateful if you could provide more detail regarding your methods and procedures at both items 13 and 14, to enable a full understanding of how this project will be carried out. The Committee was able to approve this application due to the good information provided in the Participant Information Sheet.

Please provide the Committee with copies of the updated Information Sheet and Consent Form, if changes have been necessary.

Approval is for up to three years from the date of this letter. If this project has not been completed within three years from the date of this letter, re-approval must be requested. If the nature, consent, location, procedures or personnel of your approved application change, please advise me in writing.

Yours sincerely,

Mr Gary Witte
Manager, Academic Committees
Tel: 479 8256
Email: gary.witte@otago.ac.nz

c.c. Professor R J Walker Head Medicine

9.2 Maori Consultation

NGĀI TAHU RESEARCH CONSULTATION COMMITTEE
TE KOMITI RAKAHAU KI KAI TAHU

21/08/2012 - 37
Tuesday, 21 August 2012

Dr Cutfield
Medicine
Dunedin

Tena koe Dr Cutfield

Title: Vestibular Function in Acoustic Neuroma and after Gentamicin.

The Ngai Tahu Research Consultation Committee (The Committee) met on Tuesday, 21 August 2012 to discuss your research proposition.

By way of introduction, this response from the Committee is provided as part of the Memorandum of Understanding between Te Rūnanga o Ngai Tahu and the University. In the statement of principles of the memorandum, it states "Ngai Tahu acknowledges that the consultation process outlined in this policy provides no power of veto by Ngai Tahu to research undertaken at the University of Otago". As such, this response is not "approval" or "mandate" for the research, rather it is a mandated response from a Ngai Tahu appointed committee. This process is part of a number of requirements for researchers to undertake and does not cover other issues relating to ethics, including methodology; they are separate requirements with other committees, for example the Human Ethics Committee, etc.

Within the context of the Policy for Research Consultation with Maori, the Committee base consultation on that defined by Justice McGechan:

> *"Consultation does not mean negotiation or agreement. It means: setting out a proposal not fully decided upon; adequately informing a party about relevant information upon which the proposal is based; listening to what the others have to say with an open mind (in that there is room to be persuaded against the proposal); undertaking that task in a genuine and not cosmetic manner. Reaching a decision that may or may not alter the original proposal."*

The Committee considers the research to be of importance to Maori health.

The Committee notes and commends that ethnicity data is to be collected as part of the research project and recommends the use of the questions on self-identified ethnicity and descent, these questions are contained in the 2006 census.

The Ministry of Health website http://www.health.govt.nz/publications contains a list of Maori health publications. The Committee recommends you review the Maori health publications on this website, eg. Unequal Impact II: Maori and Non-Maori Cancer Statistics by Deprivation and Rural-Urban Status 2002-2006 and Tatau Kahukura: Maori Health Chart Book 2010. Another Publication, Hauora: Maori Standards of Health IV (2000-2005), has its own website, http://www.hauora.maori.nz/. These publications provide information on a range of Maori health issues and will assist in ensuring your research has an appropriate Maori health focus.

The Ngāi Tahu Research Consultation Committee has membership from:

Te Rūnanga o Ōtākou Incorporated
Kāti Huirapa Rūnaka ki Puketeraki
Te Rūnanga o Moeraki

NGĀI TAHU RESEARCH CONSULTATION COMMITTEE
TE KOMITI RAKAHAU KI KAI TAHU

The Committee suggests dissemination of the research findings to Maori health organisations regarding this study.

We wish you every success in your research and the Committee also requests a copy of the research findings.

This letter of suggestion, recommendation and advice is current for an 18 month period from Tuesday, 21 August 2012 to 21 February 2014.

The recommendations and suggestions above are provided on your proposal submitted through the consultation website process. These recommendations and suggestions do not necessarily relate to ethical issues with the research, including methodology. Other committees may also provide feedback in these areas.

Nahaku noa, na

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The Ngāi Tahu Research Consultation Committee has membership from:

Te Rūnanga o Ōtākou Incorporated
Kāti Huirapa Rūnaka ki Puketeraki
Te Rūnanga o Moeraki

9.3 Information Sheet

Information Sheet

Vestibular Function in Vestibular Schwannoma

Researchers: Isaac Tranter-Entwistle, Medical Student; Dr Nick Cutfield, Neurology; A/Prof Patrick Dawes, ENT; A/Prof Cynthia Darlington, Pharmacology

Thank you for considering taking part in this research study. Please read this information sheet before deciding to participate.

The study will compare two measures of balance function in people who have been diagnosed with vestibular schwannoma. One measure is well established the other is new. If the new measure is accurate it could be used to test balance function more easily. This information could influence clinical management, such as whether one treatment may be more appropriate than another. Measurements of the test will be completed using eye-video recording and caloric testing.

If significant vestibular function is detected you will be invited to undergo assessment of spatial memory and various cognitive tasks.

Principal investigators

This study is being conducted by Isaac Tranter-Entwistle Medical Student and BMedSci candidate, Dr Nick Cutfield, Consultant Neurologist, A/Prof Patrick Dawes, ENT surgeon and A/Prof Cynthia Darlington.

What kind of participants are sought?

The study will only involve people who are known to have a vestibular schwannoma

What does being in the study involve?

You will travel to the ENT and neurology departments at the hospital and your cost of travel will be reimbursed. We would like you to bring a support person with you if you wish. You will undergo a 10 minute test wearing video goggles and undergo small side to side head movements: "video head impulse testing". This will take about 10 minutes. Then you will have

a caloric test. Caloric testing is a standard clinical test that has been in used for about 50 years. Warm (44 deg) or cool (30 deg) water will be run into your ear canal. This will stimulate the balance organ of that ear and make you fell dizzy (a spinning sensation). Once again video goggles will be used to record your eye movements. The test will take about 40 minutes including breaks. A hearing test may be required, this is a routine clinical test and may take up to 30 minutes; you will have done this test beforehand. You will also complete a balance symptom scores questionnaire. This may take 10 minutes. The test will take no more than two hours total, including short breaks.

The clinical supervisors Dr Nick Cutfield, consultant neurologist; A/Prof Patrick Dawes and Isaac Tranter-Entwistle, medical student at Dunedin Hospital will examine your medial records at Dunedin Hospital and any MRI brain scans you have had for the specific purpose of reviewing your diagnosis and measuring the size of your vestibular schwannoma.

You will be asked to consent to being contacted if further tests or clinical appointments are thought helpful as a result of this study.

Benefits, Risks and Safety

The caloric test may cause some mild ear discomfort, dizziness and/or nausea.

There are no direct benefits to you if you take part in the study. However, the aim of this study is to determine if the video enhanced head impulse test is a viable measure of vestibular function. We hope that this will help patients and clinicians in the future by helping to better inform clinical management for your condition.

Confidentiality

The data collected will be securely stored to protect your privacy. In keeping with university policies, any raw data (including scan results and questionnaire scores) will be retained in secure storage for five years after the results of the study are published. After this period it will be destroyed. Any details that might identify you will be removed before the study data is analysed.

9.4 Consent Form

Southern District Health Board

University of Otago

Consent Form

Vestibular Function in Vestibular Schwannoma

Researchers: Isaac Tranter-Entwistle, Medical Student; Dr Nick Cutfield, Neurology; A/Prof Patrick Dawes, ENT; A/Prof Cynthia Darlington, Pharmacology

I have read the Information Sheet concerning this project and understand what it is about. All my questions have been answered to my satisfaction. I understand that I am free to request further information at any stage. I understand:

1. My participation in the project is entirely voluntary;
2. I am free to withdraw from the project at any time without any disadvantage. If I do not participate in the study this will not affect my clinical care in any way.
3. Results from my tests done during this study that may be helpful to my future health care will be recorded in my clinical notes. Data stored or analysed in University areas will have personal identifying information removed. Raw data which has a direct relationship to the project results will be retained in secure storage for at least five years.
5. Caloric testing done during this project is an established clinical test but can cause mild ear discomfort, dizziness and/or nausea.
6. The results of the project may be published in scientific journals and will be available in the University of Otago Library (Dunedin, New Zealand) but every attempt will be made to preserve my anonymity.

I agree to take part in this project.

....

(Signature of participant) (Date)

This study has been approved by the University of Otago Human Ethics Committee. If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479 8256). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.

9.5 Dizziness Handicap Inventory

Dizziness Handicap Inventory

The purpose of this scale is to identify difficulties that you may be experiencing as a result of your dizziness. Please answer Yes, No or Sometimes. **Answer each question as it pertains to your dizziness only.**

1. Does looking up increase your problem?	Yes	Sometimes	No
2. Because of your problem, do you feel frustrated?	Yes	Sometimes	No
3. Because of your problem, do you restrict your travel for business or recreation?	Yes	Sometimes	No
4. Does walking down the aisle of a supermarket increase your problem?	Yes	Sometimes	No
5. Because of your problem, do you have difficulty getting into or out of bed?	Yes	Sometimes	No
6. Does your problem significantly restrict your participation in social activities such as going out to dinner, going to movies, dancing, or to parties?	Yes	Sometimes	No
7. Because of your problem, do you have difficulty reading?	Yes	Sometimes	No
8. Does performing more ambitious activities like sports, dancing, household chores such as sweeping or putting dishes away increase your problem?	Yes	Sometimes	No
9. Because of your problem, are you afraid to leave home without having someone with you?	Yes	Sometimes	No
10. Because of your problem, have you been embarrassed in front of others?	Yes	Sometimes	No
11. Do quick movements of your head increase your problem?	Yes	Sometimes	No
12. Because of your problem, do you avoid heights?	Yes	Sometimes	No
13. Does turning over in bed increase your problem?	Yes	Sometimes	No
14. Because of your problem, is it difficult for you to do strenuous housework or yard work?	Yes	Sometimes	No
15. Because of your problem, are you afraid people may think you are intoxicated?	Yes	Sometimes	No
16. Because of your problem, is it difficult for you to go for a walk by yourself?	Yes	Sometimes	No
17. Does walking down a sidewalk increase your problem?	Yes	Sometimes	No
18. Because of your problem, is it difficult for you to concentrate?	Yes	Sometimes	No
19. Because of your problem, is it difficult for you to go for a walk around your house in the dark?	Yes	Sometimes	No
20. Because of your problem, are you afraid to stay home alone?	Yes	Sometimes	No
21. Because of your problem, do you feel handicapped?	Yes	Sometimes	No
22. Has your problem placed stress on your relationship with members of your family or friends?	Yes	Sometimes	No
23. Because of your problem, are you depressed?	Yes	Sometimes	No
24. Does your problem interfere with your job or household responsibilities?	Yes	Sometimes	No
25. Does bending over increase your problem?	Yes	Sometimes	No