DELAYED HEARING LOSS FOLLOWING VESTIBULAR SCHWANNOMA SURGERY:

Behavioural and electrophysiological responses in the early postoperative period

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ABSTRACT

Some patients suffer hearing loss in the early postoperative period following vestibular schwannoma excision despite having intact hearing immediately after surgery. As this phenomenon has rarely been documented or described, the putative mechanism remains vague. The objective of the current study was to document the patterns of change in behavioural and electrophysiological responses in patients following VS surgery to better describe the phenomenon of delayed hearing loss. In particular, we aimed to determine whether the impairment that eventually leads to delayed hearing loss is neural or cochlear in origin.

Auditory function was monitored in six adult patients who underwent surgery at Christchurch Public Hospital for excision of unilateral vestibular schwannoma through the retrosigmoid approach. Patients were assessed pre- and postoperatively by pure-tone audiometry, speech audiometry, tympanometry, distortion product otoacoustic emissions (DPOAEs), and auditory brainstem response (ABR). When measurable hearing was demonstrated postoperatively, pure-tone audiometry, speech audiometry and ABR were assessed at 24 hour intervals following surgery. Transtympanic electrocochleography (ECochG) was carried out if wave I of the ABR was lost during the postoperative period.

Postoperative monitoring revealed that 4 patients suffered permanent anacusis and the remaining 2 patients had permanent hearing preservation. There were no patients who

experienced delayed hearing loss in the early postoperative period. A phenomenon similar to delayed hearing loss was observed in case 2 who demonstrated loss of ABR wave I on the 7^{th} postoperative day. Postoperative ECochG recorded in this case showed an enhanced negative SP on the operated side. The findings of this study are discussed in detail with particular reference to the underlying pathophysiology.

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1. INTRODUCTION

The widespread use of sophisticated diagnostic testing, such as magnetic resonance imaging, has facilitated early detection of vestibular schwannoma (VS) in a higher proportion of patients. Because these patients tend to have smaller tumours, they present with better hearing preoperatively. In an effort to preserve residual hearing, various refinements in micro-surgical technique have been introduced. Despite this, the majority of patients that undergo hearing conservation surgery have no measurable hearing on the affected side following VS excision (Samii & Matthies, 1997).

With the recent introduction of intraoperative auditory system monitoring, the aetiology of hearing loss associated with VS surgery is better understood. Postoperative deafness following VS excision is commonly attributed to complete obstruction of the arterial blood supply or dissection of the cochlear nerve during tumour removal (Colletti, Fiorino, Carner, & Tonoli, 1997). Consequently, complete loss of auditory function immediately following surgical injury is expected and has frequently been demonstrated. However, several studies have reported cases of delayed hearing loss in the early postoperative period despite having intact hearing immediately after surgery (Fahlbusch, Neu, & Strauss, 1998; Neu, Strauss, Romstock, Bischoff, & Fahlbusch, 1999; Palva, Troupp, & Jauhiainen, 1985; Strauss et al., 2001; Strauss et al., 1991). Similarly, anecdotal reports of rapid hearing deterioration following VS excision via the retrosigmoid approach have been made by surgeons at Christchurch Public Hospital (P. Bird, personal communication, November 19, 2006). As this phenomenon remains relatively unknown, few studies have attempted to document or

describe patterns of initial hearing loss following surgery (Strauss et al., 1991). In particular, patterns of change in postoperative electrophysiological responses associated with the phenomenon of delayed hearing loss have not been well described in the literature. For this reason the mechanism responsible for postoperative delayed hearing loss remains vague.

The aim of this study was to document the time course of changes in behavioural and electrophysiological responses in patients suffering delayed hearing loss following VS excision. The postoperative pattern of hearing loss has been documented to provide valuable information regarding real-time detection of the hearing loss, the time course of damage and the likely site of impairment. In particular, we aimed to determine whether the site of impairment that ultimately leads to delayed hearing loss is neural or cochlear. This information will be used to determine the possible cause of delayed hearing loss, leading to better clinical outcomes through improved surgical technique and medical treatment.

1.1. The peripheral auditory pathway: Afferent transmission

Auditory processing begins with the pinna and transmission of airborne vibration through the ear canal. Sound waves that enter the ear canal vibrate the tympanic membrane and are transmitted through the middle ear and oval window to the cochlear fluids, with a resultant displacement of the basilar membrane. High frequency waves stimulate more basal portions of the cochlea, while low frequency waves stimulate more apical regions (von Bekesy, 1960). This occurs due to the gradual decrease in stiffness of the basilar membrane from base to apex. In the organ of Corti, displacement

of the basilar membrane in the direction of the reticular lamina causes radial shearing of the outer hair cell (OHC) stereocilia allowing an influx of potassium ions from the endolymph in scala media that depolarise the cell. This receptor potential triggers active contractions of the cell body, increasing the vibration of the basilar membrane (Brownell, Bader, Bertrand, & de Ribaupierre, 1985). The OHC active process is responsible for canceling friction of the traveling wave along the basilar membrane vibration, sharpening the traveling wave, and, enhancing cochlear sensitivity and frequency selectivity for low intensity stimuli (Dallos, 1992). Shearing of the inner hair cell (IHC) stereocilia (due to fluid flow caused by basilar membrane vibration) results in depolarisation of the IHC which triggers the release of neurotransmitter (glutamate), generating an action potential in the afferent nerve endings of the corresponding spiral ganglion cells (SGCs). The axons of the SGCs are bundled together to form the cochlear portion of the eighth cranial nerve. Neural discharge is tonotopically preserved as it travels through this nerve; high frequency fibres are located around the outside of the nerve trunk and low frequency fibres in the core (Sando, 1965) as shown in Figure 1. Cochlear nerve fibres can be divided into two groups. Type I fibres make up approximately 90% of all cochlear nerve fibres. These fibres connect to the IHC and are thick and myelinated. The remaining cochlear nerve fibres, termed type II fibres connect with the OHCs, are thinner in diameter and unmyelinated (Musiek & Baran, 2007). The SGC is a bipolar neuron and its central axon terminates at the cochlear nucleus, located in the lower brainstem. Neural impulses from the peripheral nervous system are conveyed to the central nervous system at this location.

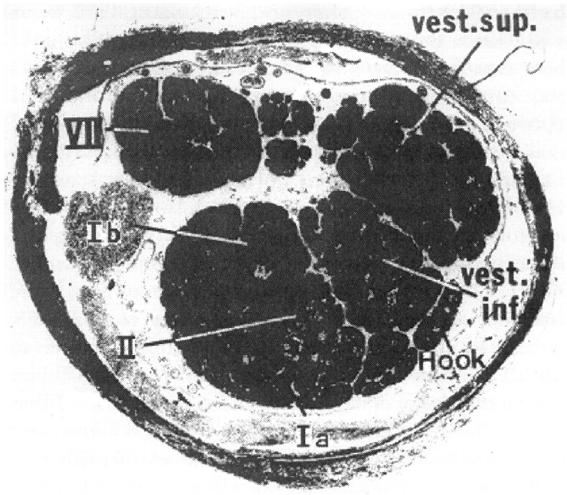


Figure 1. Tonotopic arrangement of the human cochlear nerve showing the position of the facial nerve (VII), the superior division of the vestibular nerve (vest. sup.), the inferior division of the vestibular nerve (vest. inf.) and the cochlear nerve with the nerve fibres for the most basal end (Hook), for the lower basal turn (Ia), the upper basal turn (Ib) and the second and apical turns (II) (from Spoendlin & Schrott, 1989).

1.2. The peripheral auditory pathway: Efferent transmission

The peripheral auditory pathway described above is part of the afferent system which carries messages from the cochlea to the auditory cortex. Efferent projections from the auditory cortex to the cochlea also play a role in the perception of sound. Two separate anatomic divisions of the efferent auditory system have been described (Warr, 1992; Warr & Guinan, 1979):

1. The medial olivocochlear (MOC) fibres are thick myelinated nerve fibres that originate in or near the medial superior olivary (MSO) nucleus complex. The majority of these fibres (75%) synapse directly with the OHCs of the contralateral cochlea while the remaining fibres synapse with ipsilateral OHCs.

2. The lateral olivocochlear (LOC) fibres are thinner unmyelinated nerve fibres that originate in or near the lateral superior olivary (LSO) nucleus complex. The majority of LOC neurons (89%-91%) connect with afferent type I dendrites immediately beneath the ipsilateral IHCs.

Although the role of the efferent auditory system is not fully clear, evidence to date indicates that this feedback system modulates peripheral auditory input. A number of studies have demonstrated that contralateral stimulation of the medial system has an inhibitory effect on cochlear output by modulating basilar membrane movement (Collet et al., 1990; Folsom & Owsley, 1987; Gifford & Guinan, 1987; Guinan, 2006; Komazec, Filipovic, & Milosevic, 2003). As selective disruption of the lateral system is more difficult to achieve, much less is known about this pathway. However, recent studies have demonstrated that when activated the LOC system elicits either slow excitation or slow suppression of cochlear nerve output (Groff & Liberman, 2003). A number of studies have reported that the net effect of LOC innervation seems to be excitatory (Le Prell, Halsey, Hughes, Dolan, & Bledsoe, 2005). This ability of efferent pathways to modulate both cochlear and cochlear nerve excitability may reduce vulnerability to acute acoustic injury (Darrow, Maison, & Liberman, 2007).

1.3. The internal auditory canal

Afferent and efferent fibres have a similar anatomic location within the peripheral auditory system, both forming part the eighth cranial nerve. The eighth cranial nerve consists of the cochlear nerve, and the superior and inferior vestibular nerves. As noted

previously, the cochlear nerve, which consists of type I and type II afferent nerve fibres transmits information about hearing from the cochlea to the brain. The vestibular nerve conveys information concerning balance from the semicircular canals, utricle and saccule of the inner ear to the brain. The cochlear nerve arises from within the cochlea, where the ganglion cells of the cochlear nerve fibres converge in Rosenthal's canal and then collect to form the trunk of the modiolus (Musiek & Baran, 2007). The cochlear nerve is then joined by the vestibular nerve before entering the internal auditory canal (IAC) at the fundus.

The IAC runs in a lateral to medial direction through the temporal bone of the skull and is typically 9 mm in length and 4 mm in diameter (Agirdir et al., 2001). As shown in Figure 2, the IAC encases both the eighth cranial nerve and the seventh cranial (facial) nerve. Although there is some variation in the anatomy of the eighth cranial nerve among individuals, it typically exists as three separate functionally divided nerves only at the most lateral portion of the canal. The cochlear and vestibular nerves usually fuse 3-4 mm from the lateral end of the IAC to form a nerve that is crescent shaped in cross section, becoming more tubular as it passes through the medial portion of the canal (Rubinstein, Sandberg, & Cajade-Law, 1996). Because the nerves within the IAC rotate slightly as they approach the brainstem, they do not maintain the same spatial relationship throughout the canal (Silverstein, 1984). As the eighth cranial nerve and facial nerve leave the IAC, they course through a recess known as the cerebellopontine angle (CPA), entering the brainstem at the lateral, posterior pontomedullary junction to provide input to the cochlear nucleus (Musiek & Baran, 2007).

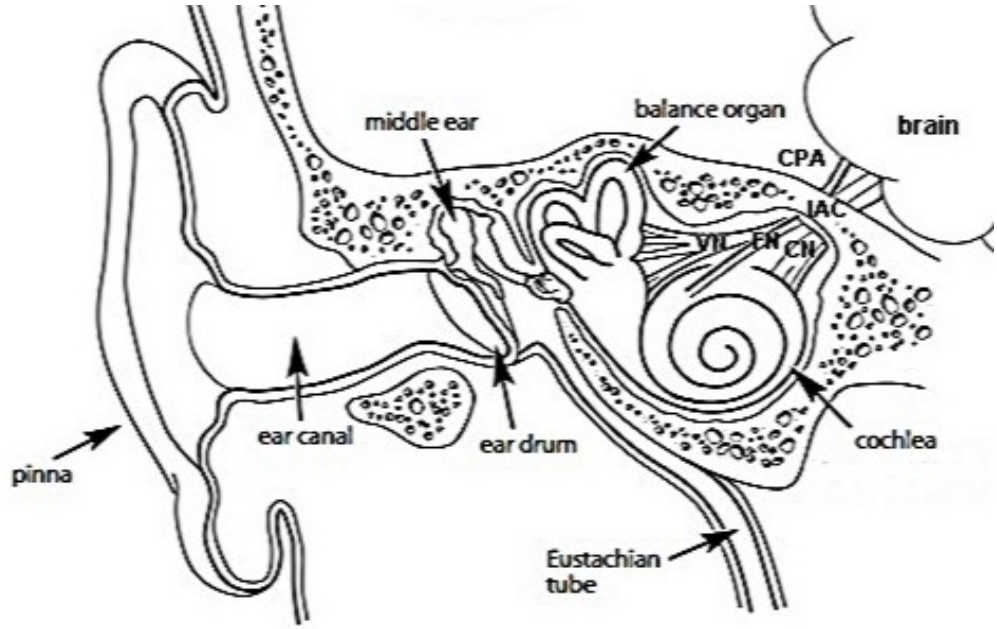


Figure 2. Peripheral auditory system. The facial nerve (FN), vestibular nerve (VN) and cochlear nerve (CN) pass through the internal auditory canal (IAC) and cerebellopontine angle before entering the brainstem.

As noted above, the efferent fibres also form part of the eighth cranial nerve. The MOC and LOC fibres exit the brainstem together and proceed laterally around the vestibular nerve root and then run with the vestibular fibres through the IAC. The efferent fibres cross over to the cochlea via the vestibulocochlear anastamosis and enter the cochlea between its first (basal) turn and second turns via the habenula perforata (Musiek & Baran, 2007).

1.4. Vascular supply to the cochlea and cochlear nerve

Accompanying the cranial nerves through the IAC is the internal auditory artery (IAA); the primary blood supply to the cochlea, vestibular system, facial nerve and eighth

cranial nerve. Several authors have reported that the IAA and its main branches are frequently found on the surface of the eighth nerve (Fisch, Dobozi, & Greig, 1972; Matsunaga, Kanzaki, & Hosoda, 1996). In addition, Matsunaga et al. (1996) reported that the main branch of the IAA was often found within the endoneurium of the cochlear nerve. They also confirmed that the blood vessels supplying the nerve or vasa nervorum consisted of vessels of arteriolar size or smaller running in a longitudinal direction within the nerve with many interconnecting branches, as shown in Figure 3.

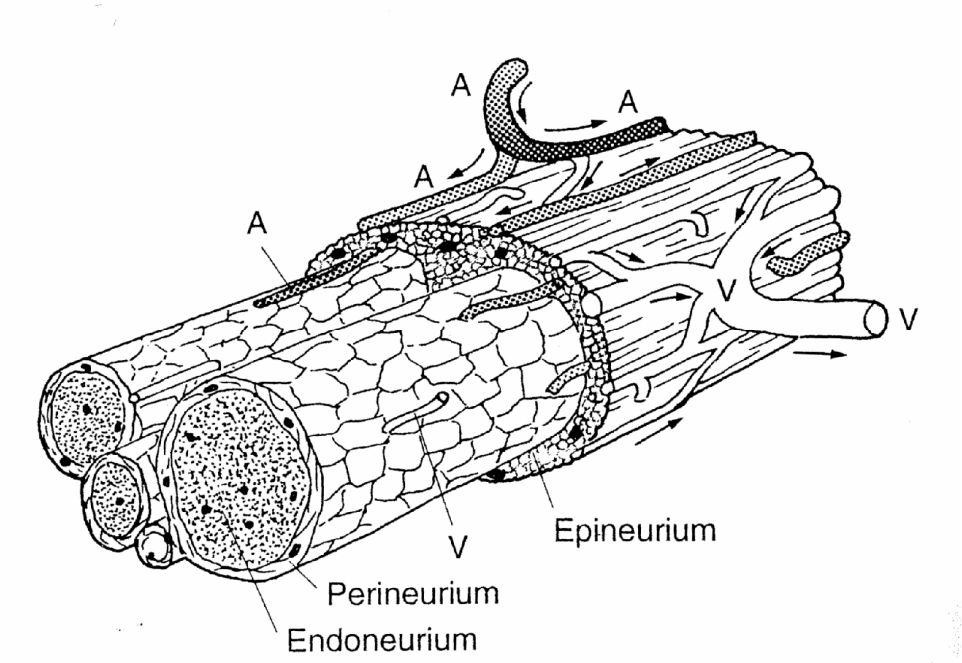


Figure 3. Schematic drawing of a peripheral nerve segment and associated vascular supply. The arterioles (A) and venules (V) are shown (from Nordin & Frankel, 2001).

The IAA itself proceeds laterally across the CPA and into the IAC. The common cochlear artery branches from the IAA near the site where the cochlear nerve penetrates into the modiolus. Arising from the common cochlear artery is the spiral modiolar artery which primarily supplies the apex of the cochlea (Axelsson & Ryan, 2001). The

cochlear branch of the vestibulocochlear artery arises after the spiral modiolar artery and supplies the proximal part of the base of the cochlea. The two arteries supplying the cochlea progressively branch to form a fine network of arterioles that supply the various structures within the cochlea. In particular, an extensive and complex capillary network supplies the stria vascularis which is responsible for maintaining endocochlear potential (Axelsson & Ryan, 2001).

1.5. Vestibular schwannoma

Vestibular schwannomas are one of the most common types of brain tumour, affecting one out of every 100,000 individuals each year (Nestor, Korol, Nutik, & Smith, 1988). This is a benign tumour arising from Schwann cells of the vestibular division of the eighth cranial nerve within the IAC or less commonly, within the CPA cistern. The tumour originates from an overproduction of Schwann cells, which normally wrap around nerve fibres to support and insulate nerves (Tallan, Harner, Beatty, Scheithauer, & Parisi, 1993). The vast majority of VS (95%) are unilateral (Nestor, Korol, Nutik, & Smith, 1988). The remaining 5% constitute bilateral tumours associated with neurofibromatosis type II, a rare genetic disorder of the nervous system.

Although VSs are histologically benign, they have the potential to be life threatening through compression and damage to adjacent cranial nerves and the brainstem. As a VS grows, it presses against the eighth cranial nerve causing hearing loss (on the affected side), tinnitus and vertigo. It may also press against the seventh (facial) nerve causing facial weakness. As the tumour enlarges towards the brain, it protrudes from the IAC

into the CPA. Further tumour growth can interfere with the trigeminal nerve, resulting in facial numbness. With continued growth, the tumour can eventually press against the brainstem (as shown in Figure 4) and cerebellum and become life threatening.

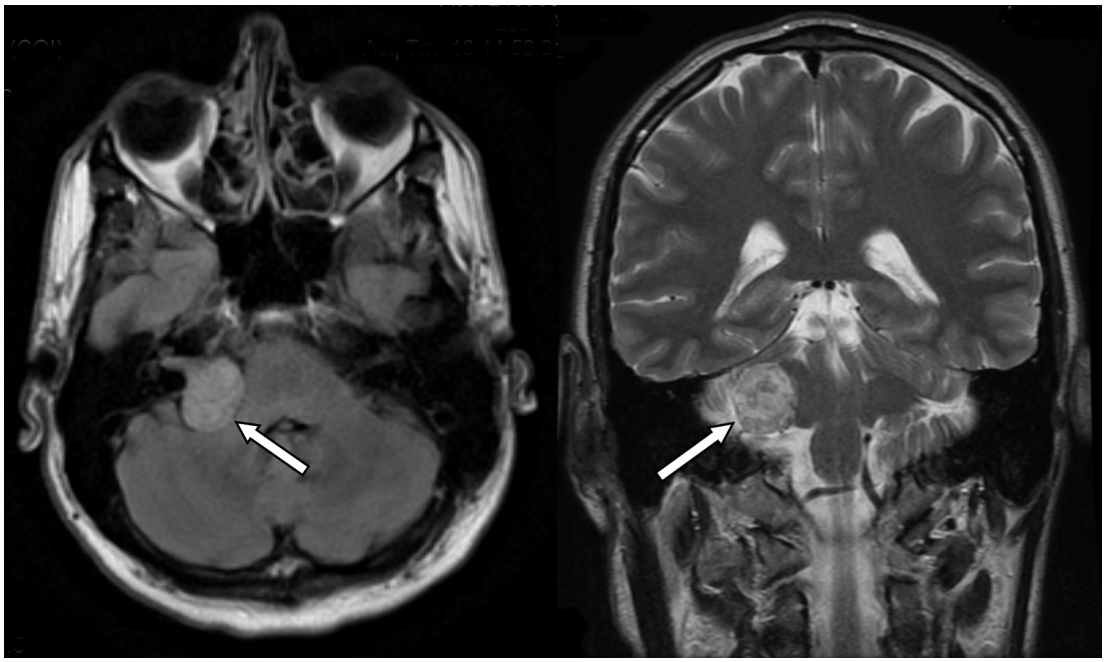


Figure 4. Preoperative magnetic resonance images showing vestibular schwannoma (arrow) exerting pressure on the brain stem.

The definitive diagnostic test for the presence of a VS is magnetic resonance imaging (MRI) (House, Waluch, & Jackler, 1986; Mikhael, Wolff, & Ciric, 1987). Depending on preoperative hearing levels, tumour size and location, a variety of surgical approaches can be used to remove the tumour. The approach selected mainly depends on surgeon's preference and experience. In patients with serviceable hearing, the retrosigmoid or middle fossa routes are preferred (Jackler & Pitts, 1992). The middle fossa approach is considered suitable for intracanalicular schwannomas with minimal extension into the CPA. The retrosigmoid approach uses a posterior fossa craniectomy

to provide good visualization of the CPA and exposure of the IAC. Through this approach, hearing and facial nerve preservation can be attempted for lesions of all sizes (Samii & Matthies, 1997).

Despite recent clinical interest and various refinements in micro-surgical technique, a large proportion of patients that undergo hearing conservation surgery continue to suffer considerable hearing loss. Postoperative hearing loss in the presence of apparent nerve preservation is believed to result from direct trauma to the cochlea or cochlear nerve, or interruption of the vascular supply to the cochlea and/or cochlear nerve (Colletti, Fiorino, Carner, & Tonoli, 1997). For this reason, intraoperative monitoring of electrophysiological responses during VS surgery is now commonly implemented. These measures can be used to correlate surgical maneuvers to the damage of auditory structures and help to determine hearing prognosis, as well as provide feedback to the surgeon to prevent this damage occurring. Indeed, several studies have reported that intraoperative monitoring of auditory potentials during VS surgery is associated with a higher rate of hearing preservation, particularly for small tumours (Harper et al., 1992; Slavit, Harner, Harper, & Beatty, 1991).

1.6. Electrophysiological measurement of auditory function

Electrophysiological measures of auditory function such as the auditory brainstem response (ABR), electrocochleography (ECochG) and otoacoustic emissions (OAEs) are used to objectively assess auditory pathway function. As these techniques were an important part of the present study, an in-depth discussion of each is warranted.

1.6.1. The auditory brainstem response

The ABR is an auditory evoked potential, utilising responses of the auditory nerve and brainstem. It reflects the synchronous auditory neural activity along the ascending auditory pathway in response to the onset of an acoustic stimulus. The ABR consists of seven waves that typically occur within 10 ms of stimulus onset (Jewett & Williston, 1971). Waves I and II represent the response from the peripheral and central portion of the cochlear nerve respectively. Subsequent waves are complex sums of contributions from multiple generators in the brainstem (Hall, 1992). Figure 5 displays a standard ABR response.

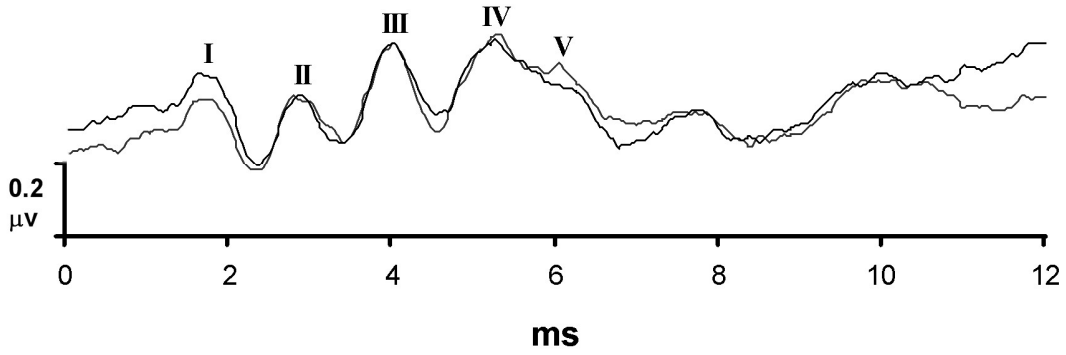


Figure 5. A standard ABR response to 80 dB nHL click stimulus. The peaks of waves I - V are labeled. Time on the abscissa is in milliseconds after stimulus onset.

Broadband acoustic transients such as brief duration clicks are commonly used as the stimulus during ABR analysis. In response to such stimuli, highly synchronized neural activation first occurs in the basal region of the cochlea due to its closer proximity and higher traveling wave velocity (Don & Kwong, 2002). Activity in more apical regions

of the cochlea is not reflected in the ABR due to phase cancellation of activity by more basal (high frequency) regions. Thus, the ABR elicited by clicks mainly reflects cochlear activation at the basal turn and is largely dependent on hearing status in the frequency region of 2 kHz and above (Hall, 1992).

Measures of latency and amplitude are the most commonly analysed response parameters of the ABR and are typically reported for the three major peaks: Waves I, III and V (Don & Kwong, 2002). Latency refers to the time interval between the stimulus onset and the peak of the waveform. Although absolute peak latency can be influenced by mechanical processes within the cochlea (Don, Ponton, Eggermont, & Kwong, 1998), it is generally considered to reflect neural conduction time and any intervening synaptic delays between the cochlea and higher brainstem. In normal hearing female subjects the latency of Wave I typically occurs 1.5 ms after stimulus onset, Wave III at approximately 3.6 ms and Wave V at around 5.4 ms for clicks presented at 90 dB nHL (Hood, 1998). In normal hearing individuals without otologic or neurologic problems, comparison of interaural peak latencies should reveal a difference of close to zero. A difference in the latency of wave V between ears of greater than 0.2 ms is indicative of retrocochlear pathology (Selters & Brackmann, 1977).

The amplitude of an ABR waveform is determined by the difference in magnitude between the peak and its subsequent trough. This component reflects the amount of synchronous neural activity contributing to the recorded response (Don & Kwong,

2002). Accordingly, ABR peak amplitude can be influenced by the size of contributions from individual neurons, the number of contributing neurons and/or the degree of synchronization among contributing neurons (Don, Ponton, Eggermont, & Masuda, 1994). Although a number of studies have reported high variability of the wave V amplitude measure, this can primarily be attributed to between-subject rather than within-subject variability (Lauter & Karzon, 1990). It should be noted however, that even with standard averaging techniques and consistent stimulus conditions, within-subject amplitude measures can be altered by variable levels of background noise and electrical interference (Don & Elberling, 1994). Controlling the destructive effects of non-stationary noise during ABR recording is therefore important when comparing amplitude variations over time for a particular subject.

1.6.2. Electrocochleography

Like the ABR, ECochG involves the recording of auditory evoked potentials. ECochG however, measures more peripheral electrical potentials generated in the cochlea and distal part of the cochlear nerve. It consists of 3 components (Don & Kwong, 2002; Hall, 1992):

1) The cochlear microphonic (CM) is an alternating current (AC) electrical potential that represents the potassium ion current flow through mainly the outer hair cells and therefore reflects the instantaneous displacement of the OHC stereocilia (Patuzzi, Yates, & Johnstone, 1989).

2) The summating potential (SP) is the direct current (DC) response that reflects the asymmetry of the IHC receptor potential, and is usually dominated by the IHCs.
3) The compound action potential (CAP) represents the summed response of the synchronous firing of numerous auditory nerve fibres leaving the cochlea in the distal part of the cochlea nerve.

Interpretation of the ECochG most commonly involves analysing component magnitude (amplitude). Although differing opinions exist regarding on how to best measure magnitude, the single point method is often adopted for simplicity (Ferraro & Durrant, 2002). In this method, the components are measured peak to trough from their leading edge. It is important to note that the CM (and stimulus artifact) can sometimes be large enough to obscure early components of the ECochG and overshadow the CAP. In order to differentiate the CM from the neural response, clicks can be presented in alternating polarity in order to cancel the CM, which is dependent on stimulus phase. This is demonstrated in the ECochG tracings displayed in Figure 6.

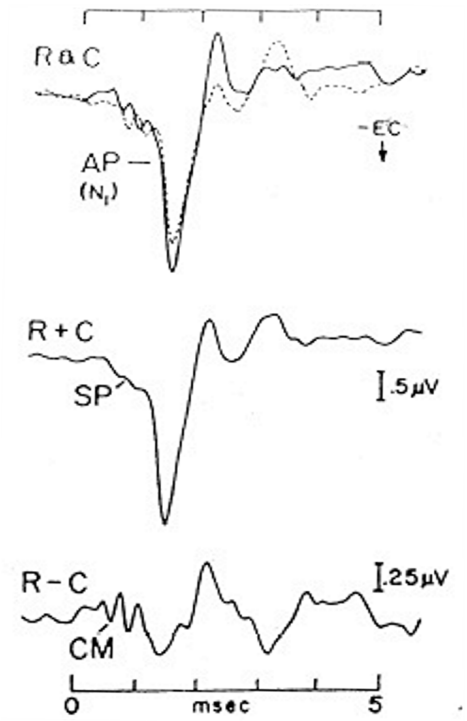


Figure 6. Components of the human electrocochleogram evoked by click stimuli. Top tracings display responses to rarefaction (R) and condensation (C) polarity clicks. Adding separate R and C responses (middle tracing) enhances the cochlear Summating Potential (SP) and auditory nerve Action Potential (AP). Subtracting R and C responses (bottom tracing), enhances the Cochlear Microphonic (CM) (from ASHA, 1988, pg. 9, based on data from Coats, 1981).

In terms of the CAP analysis, latency is also relevant. Because the CAP is effectively the same component as Wave I of the ABR, amplitude and latency of these responses are influenced in a similar manner (Moller & Jannetta, 1983). Due to differences in electrode placement however, the amplitude of the CAP is significantly larger compared to Wave I of the ABR (Bauch & Olsen, 1990; Ferraro & Ferguson, 1989). For this reason, monitoring ECochG has been found more reliable than ABR with respect to assessing cochlear function (Lenarz & Ernst, 1992; Schlake et al., 2001).

Because the CM reflects OHC integrity, while the CAP reflects activity of the afferent cochlear nerve, analysis of the ECochG makes it possible to distinguish between cochlear and peripheral neural pathology. However, as the CAP is influenced by IHC output and thus to a lesser extent the function of the OHCs, it can be difficult to confirm the presence of neural pathology if cochlear dysfunction exists. In other words, decreased CAP response does not necessarily suggest cochlear nerve impairment in cases with a reduced CM (Yokoyama, Nishida, Noguchi, & Komatsuzaki, 1999). In such cases, only invasive techniques such as electrical promontory stimulation (EPS) can be used to rule out the existence of neural dysfunction. Although EPS offers a quantitative assessment of auditory-nerve function, a variety of test variables exist, and false-negative test results have been observed in 25% of subjects (Schmidt et al., 2003).

1.6.3. Otoacoustic emissions

The noninvasive objective technique of recording OAEs represents an additional method of evaluating functional status of the cochlea. Specifically, OAEs are believed to represent electromotile activity in the OHCs (Brownell, 1990; Kemp, 1978). This measure therefore reflects the contribution of the active process within the cochlea and is not sensitive to disturbances of the afferent cochlear neurons. However, function of the OHCs can be affected by disturbances to the efferent neurons, specifically the MOC fibres, which reach the cochlea via the inferior vestibular nerve. Numerous studies have demonstrated the inhibitory effect of MOC stimulation on OAE amplitude (Guinan, 2006).

OAEs can be elicited through several different methods. Distortion product otoacoustic emissions (DPOAEs) are low-intensity sounds elicited by the normal cochlea in response to two simultaneous tones of different frequencies (f_1 and f_2). Although DPOAEs are produced at a number of frequencies, the largest amplitude response occurs at $2f_1$-f_2. The $2f_1$-f_2 response is considered by most authors to reflect hearing sensitivity at the frequency equal to the geometric mean of the primaries (Moulin, Bera, & Collet, 1994). However, others have reported that for the $2f_1$-f_2 DPOAE, the tips of the suppression tuning curves tuned consistently below the geometric-mean frequency of the primary tones (Martin, Jassir, Stagner, Whitehead, & Lonsbury-Martin, 1998).

By varying the frequency of the two primary tones, while maintaining a constant f_2: f_1 ratio, the active dynamic status of the outer hair cell system can be measured for different frequency regions within the cochlea. The frequency range for which DPOAEs can accurately identify auditory status is between 1 and 6 kHz (Hall, 2000). However, there have been reports of difficulty detecting lower frequency responses (<2 kHz) when there are elevated levels of background noise (Telischi, Widick, Lonsbury-Martin, & McCoy, 1995).

DPOAE signal to noise ratio (SNR), rather than amplitude, is considered superior at identifying hearing loss at most frequencies (Gorga et al., 1997). When behavioural thresholds are better than 20 dB HL, DPOAEs typically have a SNR of greater than 5 dB (Hall, 2000). The upper limit of hearing loss for which DPOAEs can be observed has been reported to range from 40 to 50 dB HL (Gorga, Neely, & Dorn, 1999; Harris,

1990). Harris (1990) reported that when pure-tone threshold was greater than 50 dB HL in subjects with cochlear hearing loss, DPOAEs were absent or were significantly attenuated in 94% of subjects. Likewise, Gorga, Neely, & Dorn (1999) reported sensitivity approached 100% once cochlear hearing loss exceeded 40 dB HL. Both studies noted a variable association of emission level with behavioural thresholds for patients with mild hearing losses (21 to 40 dB HL). In cases where either the degree of hearing loss is significant or a high frequency (>4 kHz) hearing loss exists, DPOAEs provide more information regarding OHC function than other OAE measures (Gorga et al., 1993).

It has been demonstrated that OHCs are extremely sensitive to ischemia and in animals; DPOAEs have proved very reliable for detecting variations in cochlear blood flow (Mom, Telischi, Martin, & Lonsbury-Martin, 1999; Widick, Telischi, Lonsbury-Martin, & Stagner, 1994). Several studies have documented use of DPOAEs to monitor real-time auditory function during cerebellopontine angle tumour removal operations in humans (Morawski et al., 2004; Telischi, Widick, Lonsbury-Martin, & McCoy, 1995). This measure was found to be a rapid indicator of cochlear damage following an interruption of cochlear blood supply during tumour removal.

Recording electrophysiological responses using the ABR, ECochG and DPOAEs provides considerable information regarding the status of the entire portion of the auditory pathway at risk during a VS operation. Monitoring these responses in patients before VS excision and during the postoperative period permits real time detection of

damage to peripheral auditory structures and more importantly, indicates the likely site of impairment. The CAP (wave I of the ABR) reflects the integrity of the auditory nerve peripheral to the tumour, wave V of the ABR is an indication of auditory nerve activity central to the tumour, and DPOAEs, the CM or the SP can be used to confirm functional status of the cochlea.

It is important to note that electrophysiological responses are not a measure of hearing in terms of the conscious perception of sound: the presence or absence of these responses does not signify preservation or loss of hearing, respectively, with complete reliability. Hearing can be normal audiometrically in patients with grossly abnormal ABRs (Legatt, Arezzo, & Vaughan, 1988). At least one case has demonstrated the complete loss of the ABR with preservation of hearing (Yamamoto, Katayama, & Tsubokawa, 1994). In such cases, there is some degree of signal transmission along the peripheral auditory pathway (to enable hearing) but nerve impulses are sufficiently desynchronized to render the ABR undetectable. For the same reason, discrepancies with deficits in word recognition ability despite normal pure-tone thresholds have long been reported in cases of auditory nerve impairment (Morlet, Dubreuil, Duclaux, & Ferber-Viart, 2003). It is therefore important to relate electrophysiological findings to behavioural responses to get an accurate picture of the patient's true auditory abilities.

1.7. Preoperative auditory function

Although hearing loss is the most common symptom associated with a VS, the vast majority of cases present with measurable hearing preoperatively (Harner, Fabry, &

Beatty, 2000). Most of these subjects tend to have a high frequency sensorineural hearing loss and serviceable word recognition. It is important to note that currently some controversy exists regarding what constitutes serviceable hearing. Most commonly it is defined as a pure tone average (PTA) at 0.5, 1 and 2 kHz of >50 dB HL with a speech discrimination score of 50% or more; generally referred to as the 50/50 rule (Brackmann, Owens, & Fayad, 2001; Gardner & Robertson, 1988). This definition will be used to describe serviceable hearing for the purpose of the current study.

In terms of electrophysiological responses, the presence of a VS is nearly always associated with significantly prolonged absolute latency values of all peaks beyond Wave I of the ABR and abnormally long interwave intervals (I-III or I-V). This finding has been attributed to the tumour exerting pressure on the cochlear nerve proximal to its cochlear end and therefore leading to delays in neural activation (Badie, Pyle, Nguyen, & Hadar, 2001). In addition, abnormally small peak amplitudes or absent waveforms are often seen in patients with VSs. Again, this may be due to the tumour exerting pressure on the auditory nerve, causing a change in transmission time and thus poorer overall synchronicity of response (Hall, 1992).

A study by Lapsiwala, Pyle, Kaemmerle, Sasse, & Badie (2002) evaluated intracanalicular pressure (ICaP) in patients with VSs preoperatively and found the ICaP directly correlated to wave V latency. This finding suggests that the pressure on the cochlear nerve from tumour growth in the IAC may contribute to the subjective hearing loss experienced by the majority of these patients. It should be noted however, that

cochlear dysfunction has also been reported in 57-100% of VS cases (Noguchi, Komatsuzaki, & Nishida, 1998; Prasher, Tun, Brookes, & Luxon, 1995; Telischi, 2000; Yokoyama, Nishida, Noguchi, & Komatsuzaki, 1999). In view of the above findings, it seems likely that this results from restricted blood flow in the IAA due to pressure exerted by the tumour within the IAC, leading to atrophy of the cochlea. Studies on animals have shown that vascular occlusion affected cochlear sensory cells with a tendency of more basal turn degeneration (Kimura, 1986). Thus, a cochlear impairment due to IAA obstruction can be expected to affect the high frequencies to a greater degree. The relative contribution of cochlear versus retrocochlear dysfunction is still unknown although it has been suggested that the majority of VS cases suffer from a combined cochlear/retrocochlear hearing loss (O-Uchi et al., 1994).

In subjects with VSs who suffer a cochlear hearing loss, wave I of the ABR may be reduced, distorted or absent despite the presence of an identifiable wave V (Cashman & Rossman, 1983; Hyde & Blair, 1981). DPOAEs are also likely to be absent for subjects with a moderate hearing loss or worse. Thus, recording the CAP and CM may represent the only method of monitoring cochlear function. Ferraro & Ferguson (1989) successfully demonstrated recording of the tympanic ECochG CAP in patients with no ABR wave I.

1.8. Postoperative auditory function

Postoperative auditory function can be described according to three patterns (Neu, Strauss, Romstock, Bischoff, & Fahlbusch, 1999). The most favorable outcome is referred to as permanent hearing preservation, where the patient retains some degree of measurable

hearing. It is important to note that although hearing is measurable, postoperative auditory function in these cases tends to be worse (Harner, Fabry, & Beatty, 2000) and may not always be serviceable. The literature dealing with hearing preservation during VS surgery is abundant and typically reports preservation rates in the range of 8 to 50% (Fischer, Fischer, & Remond, 1992; Frerebeau et al., 1987; Gardner & Robertson, 1988; Kaylie, Gilbert, Horgan, Delashaw, & McMenomey, 2001; Lassaletta, Fontes, Melcon, Sarria, & Gavilan, 2003; Magnan et al., 2002; Moffat, da Cruz, Baguley, Beynon, & Hardy, 1999; Saleh et al., 1996; Samii & Matthies, 1995, , 1997; Samii, Matthies, & Tatagiba, 1997; Sterkers, Morrison, Sterkers, & El-Dine, 1994). However, differences regarding patient inclusion criteria, choice of surgical procedure and classification of postoperative hearing make it difficult to compare outcomes of many published studies. Better preoperative hearing has been correlated with better hearing preservation rates (Brackmann et al., 2000). Tumour size/volume has also been reported as a good predictor of hearing preservation (Gjuric, Mitrecic, Greess, & Berg, 2007; Hecht, Honrubia, Wiet, & Sims, 1997). The probability of preserving hearing decreases significantly as the tumour enlarges. For patients with large tumours (>3 cm), preservation of hearing is currently considered by many authors to be unrealistic (Frerebeau et al., 1987; Hecht, Honrubia, Wiet, & Sims, 1997; Patuzzi, Yates, & Johnstone, 1989).

For the majority of patients that present with some hearing preoperatively, the most commonly observed outcome is permanent anacusis (total loss of hearing on the affected side) immediately following surgery. As noted previously, anacusis is typically attributed to complete obstruction of the arterial blood supply or dissection of the

cochlear nerve during tumour removal (Colletti, Fiorino, Carner, & Tonoli, 1997). A large study conducted by Samii & Matthies (1997) found that of 76% of cases with some preoperative hearing, 60.5% of these cases did not have any measurable hearing following VS surgery.

The third outcome, known as postoperative hearing fluctuation, is more rarely reported and results in either reversible or delayed hearing loss. "Reversible hearing loss" occurs when there is a recovery in hearing following anacusis immediately after surgery, whereas "delayed hearing loss" is used to describe a phenomenon where hearing is intact immediately following surgery but anacusis occurs in the early postoperative period. Delayed deterioration in hearing following VS surgery has seldom been documented (Fahlbusch, Neu, & Strauss, 1998; Neu, Strauss, Romstock, Bischoff, & Fahlbusch, 1999; Palva, Troupp, & Jauhiainen, 1985; Strauss et al., 2001; Strauss et al., 1991). In all cases where delayed hearing loss was observed and no further medical treatment was received, patients suffered from anacusis prior to hospital discharge. Although it is difficult to establish the true prevalence of this phenomenon due to variation in study design and inclusion criteria, the reported occurrence in the literature ranges from 13 to 24% (Fahlbusch, Neu, & Strauss, 1998; Neu, Strauss, Romstock, Bischoff, & Fahlbusch, 1999; Palva, Troupp, & Jauhiainen, 1985; Strauss et al., 1991).

1.9. Delayed hearing loss

In an effort to describe postoperative delayed hearing loss for the first time, Strauss et al. (1991) published a study examining this phenomenon and the associated

intraoperative ABR findings. In a series of 26 patients with medium to large size VSs (average tumour size: 2.8 cm) and preoperative documented hearing, 7 patients experienced delayed hearing loss. A similar study by Neu et al. (1999) was carried out to establish and classify intraoperative ABR patterns in order to identify those cases with postoperative hearing fluctuation. They examined a total of 70 patients with documented preoperative hearing and found 11 patients who suffered delayed hearing loss.

In both studies, all patients who suffered delayed anacusis in the early postoperative period experienced reversible or irreversible deterioration of the ABR during surgery as seen in Figure 7. In particular, the majority of patients experienced perioperative gradual loss of wave V with relative stability of wave I (Neu, Strauss, Romstock, Bischoff, & Fahlbusch, 1999; Strauss et al., 1991). In the study conducted by Strauss et al. (1991) a postoperative ABR response was also obtained in some but not all cases. Permanent loss of wave I before discharge was eventually observed in these cases, however, at what point this occurred is not well documented. Neu et al. (1999) did not describe their postoperative ABR findings.

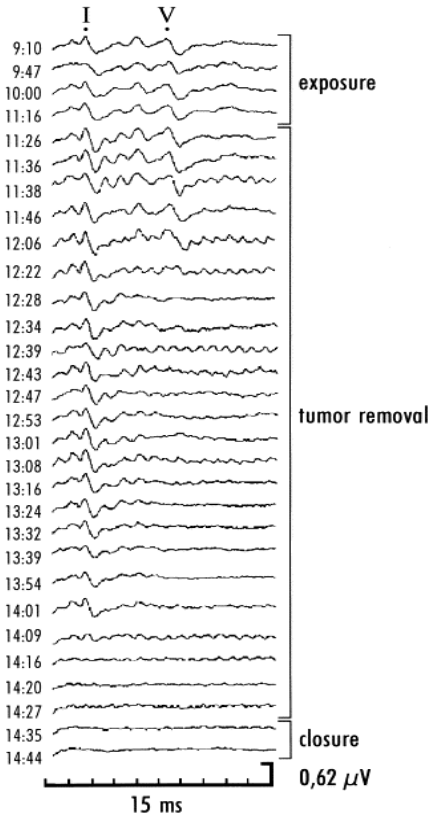


Figure 7. Deterioration of ABR potentials (wave I and V) during resection of a vestibular schwannoma (from Neu, Strauss, Romstock, Bischoff, & Fahlbusch, 1999).

The fact that hearing continues to deteriorate after surgical manipulation has ended suggests a pathophysiological mechanism initiated during surgery that continues postoperatively (Neu, Strauss, Romstock, Bischoff, & Fahlbusch, 1999; Strauss et al., 1991). As noted previously, analysis of the evoked potentials obtained during surgery can give clues to the initial site of impairment. Of particular note was the absence of intraoperative changes in latency for either Wave I or V, indicating that neural conduction velocity was not being affected during surgical manipulations. Thus, there was no further conduction impairment to nerve impulses than already caused by the presence of the tumour itself. However, fluctuations and reduction in amplitude of Wave V and less frequently Wave I was evident in all cases. This occurrence is

indicative of either a reduced number of functioning and/or responding nerve fibres or alternatively, fewer nerve fibres firing in synchrony.

The majority of patients with delayed anacusis experienced gradual loss of Wave V with relative stability of Wave I during surgery (Neu, Strauss, Romstock, Bischoff, & Fahlbusch, 1999; Strauss et al., 1991). This indicates that initially, trauma to the cochlear nerve occurred distal to the generator site of wave I. However, the eventual postoperative loss of Wave I in all patients suggests that damage to the peripheral portion of the cochlear nerve ultimately transpired. The postoperative time-course over which this occurred has not been well documented but may prove useful in terms of identifying a likely mechanism.

1.10. Proposed mechanisms leading to delayed hearing loss

Suggested mechanisms resulting in early postoperative delayed hearing loss include obstruction of the internal auditory artery (IAA) or retrograde degeneration of cochlear neurons due to either direct mechanical insult or disturbances in microcirculation (Levine, Ojemann, Montgomery, & McGaffigan, 1984; Neu, Strauss, Romstock, Bischoff, & Fahlbusch, 1999; Strauss et al., 2001; Strauss et al., 1991). Slow deterioration and eventual loss of Wave I is particularly suggestive of retrograde degeneration of the cochlear nerve (Hatayama, Sekiya, Suzuki, & Iwabuchi, 1999). This phenomenon is most likely instigated by the external force applied to the nerve during VS surgery. Retrograde degeneration may then result due to subsequent mechanical destruction of the cochlear neuroepithelium (Sekiya, Yagihashi, Asano, &

Suzuki, 2002) or transient ischemia of the nerve (Klatzo, 1975). A number of animal experiments have investigated the effect of mechanical compression on functional cochlear nerves. Shimamura et al. (2002) describe how, after compression damage occurs to the central portion of the cochlear nerve, neural degeneration proceeds retrogradely towards the spiral ganglion cells leading to disappearance of these cells altogether. External mechanical force may damage the blood-nerve barrier of the vasa nervorum of the cochlear nerve, allowing glutamate to access injured cochlear neurons directly. According to the hypothesis of excitotoxicity, glutamate causes an excessive activation of the excitatory amino acid receptors and a massive influx of calcium into the neurons (Choi, 1985). Excessive influx of calcium into injured cochlear neurons activates calcium activated enzymes and leads to spiral ganglion cell death (Choi, 1992; Sekiya, Yagihashi, Asano, & Suzuki, 2002).

Alternatively, disturbed microcirculation of the capillaries supplying the cochlear nerve due to intraoperative compression may cause postoperative hearing deterioration. The microvascular system of the peripheral portion of the eighth nerve in humans consists of sparse and large microvessels. This system maintains the ionic and osmotic balance of the endoneurial fluid, which is essential for adequate peripheral nerve function, as well as for the metabolic nourishment of the peripheral nerve fibres (Matsunaga, Kanzaki, & Hosoda, 1996). Disturbed microcirculation of the capillaries supplying the cochlear nerve can lead to massive releases of glutamate during and after nerve ischemia (Steward, 2006). As with mechanically induced degeneration, the massive release of glutamate can cause excessive influx of calcium into the injured neurons and

subsequent cell death. Sekiya & colleagues (1987; 1986) demonstrated that in dogs retraction of the eighth nerve caused a disintegration of the myelin sheath, multiple foci of petechial hemorrhage and thromboses of the blood vessels supplying the cochlear nerve. In addition to injuring the compressed portion of the cochlear nerve, damage was also found at remote sites proximal and distal to the operative site. In particular, significant damage occurred at the Obersteiner-Redlich (OR) zone; a relatively fragile and avascular portion of the cochlear nerve proximal to the site of compression. It has been proposed that such disturbances to the microvasculature, especially in the compressed region of the nerve, may aggravate postoperative nerve oedema (Sekiya, Moller, & Jannetta, 1986). It is possible that the accumulation of fluid within the confined space of the internal auditory canal could further compromise capillary circulation.

In terms of electrophysiological responses, the damage due to compression, manipulation and stretching of the central portion of the cochlear nerve can be expected to initially affect wave V (and III) of the ABR. Remote injury to the generator site of wave I due to nerve manipulation may or may not initially be apparent. However, as cochlear nerve degeneration proceeds retrogradely towards the SGCs, the generation site of wave I will also be affected leading to a decrease in amplitude and possibly the disappearance of this wave as fewer neurons respond.

Abrupt loss of perioperative ABR potentials was observed in a minority of patients with delayed hearing loss and implies sudden disturbance to the entire cochlear nerve.

Obstruction or vasospasm of the internal auditory artery (IAA) has been implicated as a possible cause of delayed hearing loss (Levine, Ojemann, Montgomery, & McGaffigan, 1984; Neu, Strauss, Romstock, Bischoff, & Fahlbusch, 1999; Strauss et al., 1991). The IAA is the principal blood supply to the cochlea as well as the vestibulocochlear nerve. Occlusion of the labyrinthine artery in guinea pigs results in a reduction of cochlear function within 45 seconds (Perlman, Kimura, & Fernandez, 1959). When occlusion time was less than 8 minutes complete recovery of cochlear responses was observed, but occlusion for 30 minutes or more resulted in incomplete recovery. As noted above, disturbances to cochlear nerve microvasculature may aggravate postoperative nerve edema. As proposed by Sekiya et al. (1986), it is possible that the accumulation of fluid within the confined space of the internal auditory canal could cause the IAA to collapse in the weeks following surgery. Sekiya et al. (1990) observed MRI changes during the first two weeks after tumour removal in humans that were suggestive of nerve edema. Vascular insufficiency due to IAA injury can be expected to result in abrupt deterioration of potentials from the cochlea (CM and DPOAEs), auditory nerve (CAP and wave I) and brainstem (wave V). Studies by Strauss et al. (1991) and Neu et al. (1999) did not carry out supplementary electrophysiological testing such as ECochG or DPOAEs making it difficult to rule out cochlear involvement and thus IAA injury.

1.11. Aims of the proposed study

Close postoperative monitoring of electrophysiological and behavioural responses is needed to define the phenomenon of postoperative delayed hearing loss more thoroughly. The current study aimed to more clearly define these mechanisms by

closely monitoring patterns of intracochlear and cochlear nerve potentials in patients during surgery and as hearing deteriorated in the early postoperative period. We aimed to determine if site of impairment eventually leading to delayed hearing loss is neural or cochlear in origin and document the time course of changes in both behavioural and electrophysiological responses. In particular, it was hoped that the inclusion of ECochG and DPOAE measures would provide evidence concerning cochlear involvement in delayed hearing loss; an important aspect that has not yet been demonstrated in the literature. Based on this information, the putative mechanism of the hearing loss can be identified and therefore avoided in future.

One of two possible outcomes was anticipated in patients suffering from delayed hearing loss:

1) In cases where retrograde degeneration of cochlear nerve fibres due to traumatic stress (either from mechanical injury or ischemia) results in delayed hearing loss, gradual damage to the cochlear nerve is expected. In these cases, the pattern of postoperative electrophysiological responses will most likely demonstrate the gradual loss of wave I and CAP with persistence of the CM, SP and possibly DPOAEs.
2) In cases where delayed hearing loss results from cochlear damage, cochlear transduction will also be affected, resulting in loss of all potentials including DPOAEs. The sudden loss of potentials from both the cochlea and cochlear nerve is most likely due to vascular impairment, particularly IAA obstruction.

2. METHOD

2.1. Participants

Between July and December 2007, a total of 6 adult patients underwent surgery at Christchurch Public Hospital for excision of unilateral vestibular schwannoma (VS) through the retrosigmoid approach. None of these patients had neurofibromatosis type II (NF2). Preoperative measurable hearing was documented in all 6 patients (3 male and 3 female). Preoperative and reproducible ABR waves I and/or V were documented in 5 cases. The age of patients ranged from 29 to 61 years with an average age of 48 years. Tumour size measured on magnetic resonance imaging (MRI) was small (maximal diameter < 15 mm) in 1 patient, medium sized (maximal diameter 15 – 29 mm) in 3 patients and large (maximal diameter > 30 mm) in 2 patients. The average tumour size measured 24 mm.

2.2. Procedure

A preoperative MRI scan was performed on all patients in order to identify the VS. Tumour size was assessed in all cases according to its maximal extrameatal diameter, as demonstrated in Figure 8. One day prior to surgery, all patients underwent a full diagnostic hearing assessment involving pure-tone audiometry, speech audiometry, tympanometry, distortion-product otoacoustic emissions (DPOAEs), and an auditory brainstem response (ABR). All preoperative testing was carried out in a sound treated room in the Audiology Department at Christchurch Public Hospital.

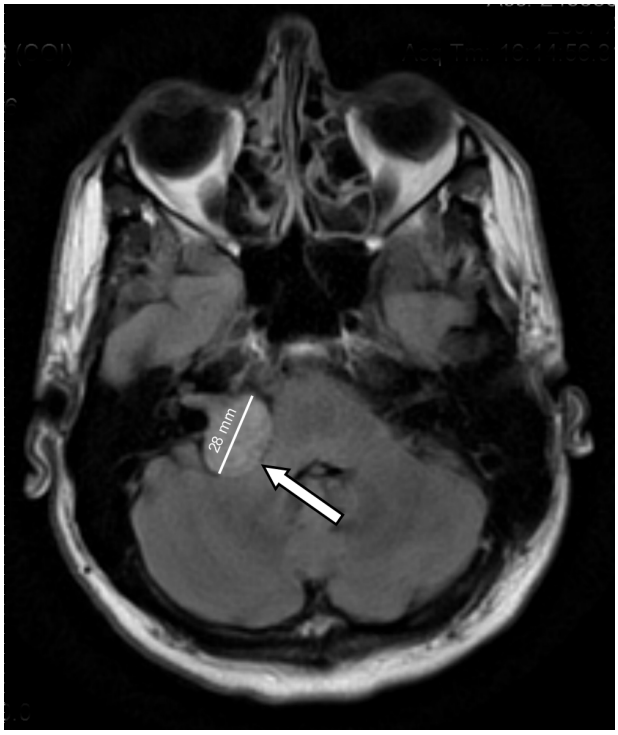


Figure 8. Preoperative magnetic resonance image (transverse view) from case 4, showing a 28 mm vestibular schwannoma exerting pressure on the brain stem. Tumour size was based on the maximal extrameatal diameter (indicated by the white line).

Immediate postoperative hearing was documented by recording an ABR approximately 3 hours following surgery. When a repeatable response was identified, ABRs were recorded at 24 hour intervals for the remaining hospitalisation (7 days on average). In cases where a repeatable response could not be recorded postoperatively, patients were retested at 24 hours following surgery (and 1 day before discharge) to confirm the absence of the ABR. Behavioural measures including pure-tone audiometry and speech audiometry were initially performed 24 hours following the operation. When measurable hearing was demonstrated, behavioural measures were carried out at 24 hour intervals for the remaining hospitalisation, providing the patient was awake and able to assist. Otoscopy and tympanometry were carried out prior to testing to rule out

any middle ear pathology. Contralateral ear measures acted as an internal control to assess the postoperative effect of anesthetic on objective measures and the ability of the subject to assist in behavioural testing. Postoperative testing was carried out in the Neurosurgery Department of Christchurch Public Hospital.

On the day prior to hospital discharge, all patients underwent another full diagnostic hearing assessment involving pure-tone audiometry, speech audiometry, immittance audiometry, distortion-product otoacoustic emissions (DPOAEs), and an auditory brainstem response (ABR). In addition, transtympanic electrocochleography (ECochG) was carried out if the patient had lost wave I of the ABR during the postoperative period. The final diagnostic assessment was conducted in the same sound treated room as the preoperative assessment.

To ensure consistency, all pre- and postoperative testing was carried out by the author. During testing in the ward, the ambient noise level was recorded with a sound level meter (IVIE IE33J, Ivie Technologies Inc., Lehi, UT, USA). On average, the ambient noise level was 35 dB SPL and never exceeded 45 dB SPL.

2.3. Pure-tone and speech audiometry measures

Hearing thresholds were measured in 5 dB steps using the modified Hughson-Westlake procedure at 250, 500, 1000, 2000, 4000 and 8000 Hz. A calibrated diagnostic audiometer (Interacoustics AD28) was used to generate pure tones presented to each ear through ER-3A insert earphones or by a Radioear B-71 bone conduction vibrator.

Pure tone average (PTA) was determined based on the threshold at 500, 1000 and 2000 Hz. Pure-tone average changes of ≥ 10 dB were considered significant.

Speech audiometry was performed using the New Zealand Recording of the CVC (Revised AB) Word Lists (National Audiology Centre, Auckland). Word lists were presented using a portable compact disc player (Aistar A5252) and calibrated audiometer (Interacoustics AD28) via ER-3A insert earphones. The speech reception threshold (SRT), defined as the lowest intensity at which 50% of words can be recognized and repeated, was determined from a performance intensity (PI) function ascertained in 15 dB steps. The word recognition score (WRS) was then established by recording the percentage of words repeated correctly when presented 40 dB above SRT or at PB Max.

2.4. ABR measurement and analysis

The ABR was collected using a commercially-available evoked potential measurement system (SmartEP, Intelligent Hearing Systems, Miami, FL). Responses were recorded differentially between self adhesive Ag/AgCl surface electrodes applied to the high midline forehead (F_Z) and the ipsilateral earlobe (A_1 or A_2). Placement of the inverting electrode on the earlobe minimized difficulties associated with post-operative testing near the site of the surgical incision, and enhanced wave I amplitude compared to mastoid placement. An electrode on the cheek was used as a ground. To minimize any electromyogenic interference, the subject was tested in supine position with head slightly raised. Lights were dimmed during testing. Prior to recording, the impedance

between any two electrodes was always less than 3000 Ω. Minimal interelectrode impedance ensures a better quality recording by limiting internal noise, reducing the effects of externally generated electrical interference and increasing common mode rejection ratios (Hall, 2006).

Rarefaction clicks presented at a rate of 21.3 clicks/sec and 100 μs in duration with instantaneous rise and fall times were used as the stimuli. Brief-duration click stimuli tend to generate a more robust and synchronous response, resulting in well-defined waveform peaks. Thus, to test the integrity of the peripheral auditory pathway, click stimuli were considered more appropriate than tone burst stimuli which are better used to test the functioning of different regions of the cochlea. The chosen stimulus rate and duration was considered optimal in terms of maximizing signal to noise ratio per unit time (Levine, Ojemann, Montgomery, & McGaffigan, 1984). These parameters also allow comparison of results with the data of Neu, Strauss, Romstock, Bischoff, & Fahlbusch (1999) and Strauss et al. (1991). Stimulus intensity was set at 80 dB HL in order to obtain maximum amplitude response without causing cochlear injury. The air-conducted stimulus was delivered to the patient through an Ear Tone ABR insert earphone. This type of transducer has low stimulus artifact, attenuates ambient noise and decreased the need for masking the asymmetric losses typical in VS patients.

Activity was amplified, filtered and sampled for 15 ms after stimulus onset with use of a laptop computer (Toshiba Satellite). Responses were band-pass filtered between 30 Hz and 3000 Hz (6 dB/octave). These filter settings were selected because they

adequately suppress measurement related artifact and noise without distorting waveform morphology, amplitude or latency (Hall, 2006). Two independently amplified (x 100 000) and averaged waveforms (of approximately 1000 to 2000 responses) were recorded for each stimulus. Appropriate contralateral masking was used to ensure that the non-test ear did not contribute to the subject's response at stimulus levels greater than 40 dB. Each trace was repeated to ensure reproducibility and reliability of the response.

The presence of individual peaks (I-V) were determined through visual inspection of the data. Where a response could be visually identified, the absolute latencies of waves I, III and V and interwave latencies were measured and compared over time. Latency changes of 0.2 ms or greater were considered to be measurably significant. Changes in peak amplitude and morphology were also used during interpretation. All measures were based on the averages of the two sets of measurements made from the individual tracings.

2.5. ECochG measurement and analysis

ECochG measurements were performed using a commercially available electrodiagnostic system (Amplaid MK 15, Milan, Italy). Prior to electrode insertion the tympanic membrane was anesthetized locally using a drop of phenol. Responses were recorded differentially between a sterilized transtympanic (TT) needle electrode that was placed through the tympanic membrane to rest on the promontory and a self adhesive surface electrode applied to the ipsilateral mastoid (M_i). The Teflon-insulated

monopolar needle electrode was placed under microscopic guidance by an experienced physician. A self adhesive Ag/AgCl surface electrode on the contralateral mastoid (M_C) was used as a ground. The needle electrode was held in position using elasticized bands attached to a support ring placed over the test ear. Prior to recording, an electrode impedance of less than 12 kΩ was established; indicating acceptable needle placement. To minimize any electromyogenic interference, the subject was tested in supine position. Lights were dimmed during testing.

The TT approach offers distinct advantages over other more noninvasive recording methods. In particular, TT ECochG provides the greatest signal to noise ratio due to the close proximity of the recording electrode to the response generators. This approach therefore requires little signal averaging (and less time) to produce a relatively large magnitude response (Hall, 2006). Consequently, some authors consider that diagnostic interpretations tend to be easier and more reliable when using a TT electrode compared to a tympanic membrane electrode (Haapaniemi, Laurikainen, Johansson, & Karjalainen, 2000).

Both clicks and tone bursts were used as stimuli. The air-conducted stimulus was delivered to the patient through supraural headphones placed in a metal shielded shell and attached magnetically to a support ring placed over the test ear. To elicit and record the CAP, clicks were presented at a rate of 7.1 clicks/sec and were 100 μs in duration with instantaneous rise and fall times. Like wave I of the ABR, the CAP is optimally elicited using a stimulus of brief duration in order to maintain synchronicity of the

response. Because frequency-specific information was not required, a click was considered appropriate. As demonstrated by Suzuki & Yamane (1982), increasing the stimulus rate beyond 10 clicks/sec may cause some adaptation of the CAP. Thus, a slower stimulus rate was chosen to enhance this component. Stimulus artifact and the CM can sometimes be large enough to obscure early ECochG components and overshadow the SP and CAP. Therefore, clicks were presented in alternating polarity to inhibit the presence of stimulus artifact and the CM, which are both dependent on stimulus phase.

In addition to click stimuli, tone bursts at 1 and 4 kHz were used for better visualization of the CM and to differentiate the SP from the CAP. The duration of the tone burst was set at 10 ms with the rise-fall time of 1 ms and a repetition rate of 9.1/sec. As described by Ferraro, Blackwell, Mediavilla, & Thedinger (Ferraro, Blackwell, Mediavilla, & Thedinger, 1994), longer duration stimuli such as tone bursts allow the SP to be extended beyond the CAP which is an onset response and therefore only appears immediately following stimulus onset. This is not the case for the SP and CM which are cochlear potentials and have stimulus-dependent durations. Alternatively, the CAP and SP can be differentiated by significantly increasing the stimulus rate. However this method is considered less reliable as there may not be complete adaptation of the CAP (Durrant, 1986). Tone-bursts were shaped using a Blackman window to maximize the frequency specificity of the stimulus by restricting spectral energy around the desired stimulus (Gorga & Thornton, 1989). Alternating onset stimuli of rarefaction and condensation polarity were used in order to demonstrate the SP. The resulting curve

was then subtracted from the response evoked by condensation clicks to obtain the CM. Finally, in order to distinguish between the CM and stimulus artifact which both follow the waveform pattern of the stimulus, a no-sound trial was run.

Stimulus intensity was set at 90 dB HL for both clicks and tone bursts. High stimulus intensity is particularly important for recording the SP which is usually only visible at high levels with this electrode configuration (Davis, Deatherage, Eldredge, & Smith, 1958). Because ECochG responses are generated prior to crossover of the auditory pathway and are of very small magnitude, masking of the contralateral ear was not required.

Activity was amplified, filtered and sampled for 5 or 15 ms after stimulus onset for click and tone burst stimuli respectively. For tone burst stimuli, the longer sample time of 15 ms was used to extend beyond the stimulus envelope so that the entire response was visible in the averaging window. Responses to click stimuli were band-pass filtered between 30 Hz and 3 kHz (6 dB/octave). For tone burst stimuli, band-pass filters were set from 5 Hz to 3 kHz for 1 kHz and from 5 Hz to 6 kHz for 4 kHz. Again, these filter settings were selected to suppress measurement related artifact and noise without distorting cochlear or neural responses (Hall, 2006). Although the SP is a DC potential, there is evidence that high-pass filter settings of up to 30 Hz have no detectable effect on this response when elicited by a click (Durrant & Ferraro, 1991). However, the SP elicited by tone burst stimuli is likely to be significantly distorted unless the high pass filter cutoff is below 10 Hz (Ferraro & Durrant, 2006). Because the CM reflects

stimulus polarity and frequency, the low pass filter setting had to be increased with stimulus frequency to adequately encompass the response and avoid any phase distortion. An amplified (x50 000) and averaged waveform of approximately 1000 responses was recorded for each stimulus.

Recorded potentials were identified through visual inspection and changes in CAP, SP and CM amplitude and/or morphology were analysed. The absolute latency of the CAP peak was also determined and compared over time. For responses to alternating click stimuli, the SP amplitude was measured from the pre-stimulus baseline to its intercept with CAP or its peak to trough amplitude (whichever was larger). The CAP amplitude was measured from the pre-stimulus baseline to its maximum peak (the most negative point), as shown in Figure 9.

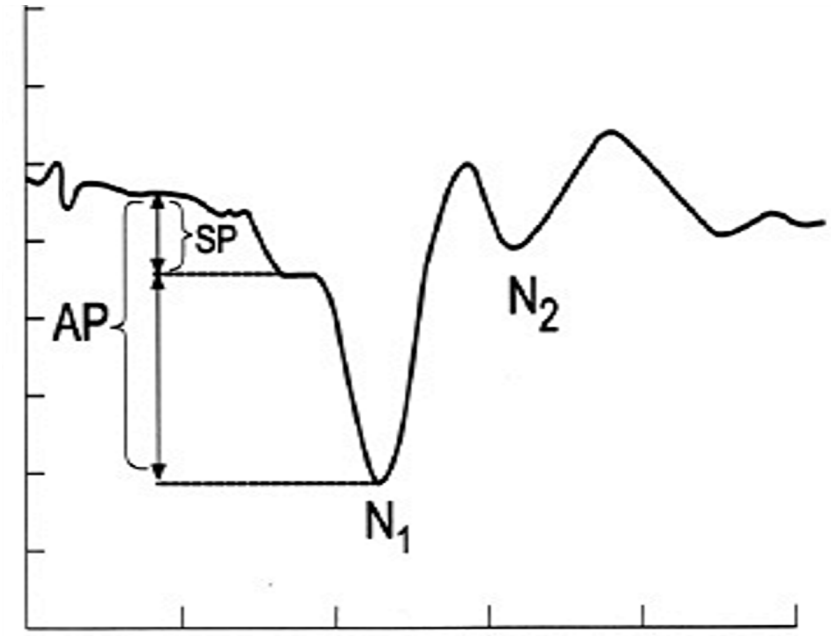


Figure 9. The magnitudes of the summating potential (SP) and compound action potential (AP) were measured with reference to the baseline value (adapted from Ferraro 2000).

For responses to tonal stimuli, the SP peak amplitude was measured as the average negative (or positive) deviation at the midpoint of the SP duration when compared to the pre-stimulus baseline, as shown in Figure 10. This method represents a compromise between avoiding the CAP at stimulus onset and maximum decay of the SP at stimulus offset (Ferraro, Blackwell, Mediavilla, & Thedinger, 1994). The CM amplitude was determined by measuring the potential from peak to peak. The degree of cochlear function was determined by comparing the measured CAP, SP and CM values with published normative data (Gibson, 1993) as well as the non-lesioned ear.

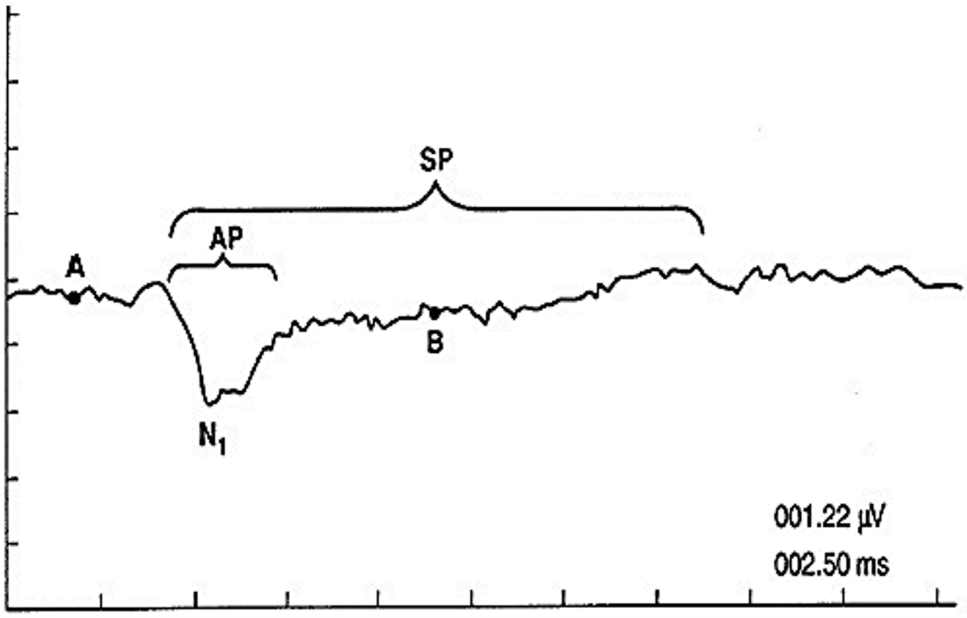


Figure 10. Amplitude of the summating potential (SP) to tone burst stimuli was measured at the midpoint of response (point B), with reference to the baseline value (point A) (from Ferraro, Blackwell, Mediavilla, & Thedinger, 1994).

2.6. DPOAE measurement and analysis

DPOAEs were elicited and recorded using a commercially available evoked potential measurement system (GSI 60, Grason-Stadler, Inc., Milford, N.H). The intensity levels of the primary frequencies were fixed at f_1 =65 dB SPL and f_2= 55 dB SPL with a frequency ratio of f_2/f_1 at 1.22. This ratio was used because in humans it has been shown to generate maximum distortion (Gaskill & Brown, 1990). The amount of distortion produced also varies with overall level and the level difference between the two primary tones (L_1-L_2). Although DPOAEs tend to increase with increasing overall level, there is considerable evidence to suggest that responses elicited to high intensity primary tones (>75 dB SPL) reflect passive cochlear processes (Dorn et al., 2001; Whitehead, Lonsbury-Martin, & Martin, 1992). Thus, moderate level primaries are considered most suitable and are more effective for identifying hearing loss. When L_1 is equal to 65 dB SPL, a level difference of 10 dB has been found to produce the largest DPOAE amplitudes in humans for geometric mean frequencies of 1 and 2 kHz whereas a level difference of 5 dB is optimal for a geometric mean of 4 kHz (Hauser & Probst, 1991).

The frequency of f_2 varied from 1.0 to 6.0 kHz in half-octave steps. DPOAE amplitudes were calculated based on the average of 16 or 32 emission samples for high and low frequencies respectively. DPOAEs were recorded as DP-grams. DPOAEs were considered present if the signal to noise ratio was greater than 5 dB and absolute amplitude greater than -10 dB SPL (Hall, 2000). Using signal to noise ratio as a form of

measurement is considered superior at identifying hearing loss at most frequencies (Gorga et al., 1997).

2.7. Interpretation of results

The patterns of electrophysiological and behavioural responses in cases of postoperative delayed hearing loss were described and evaluated in detail on a case-by-case basis. Results from each individual subject were clear enough to draw conclusions regarding the mechanism of hearing loss in that subject based on the time course and site(s) of impairment.

2.8. Ethical Considerations

Ethical approval from the Upper South A Regional Ethics Committee (Ref: URA/07/03/017) and the University of Canterbury Human Ethics Committee (Ref: 2007/45) was granted on 22 May 2007 (Appendix I). The participant's written consent was obtained prior to testing (Appendix I), and patient confidentiality was maintained in accordance with the above named ethics committees.

3. RESULTS

3.1. Permanent anacusis

From a series of a 6 consecutive patients who underwent surgery at Christchurch Public Hospital for excision of unilateral VS, 4 patients suffered permanent anacusis postoperatively. Table 1 displays a summary of the pre- and postoperative data for these patients including:

i) patient age
ii) tumour size
iii) pure-tone average (PTA)
iv) word recognition score (WRS)
v) presence or absence of DPOAEs
vi) ABR peak latencies, where available; and
vii) whether anatomic cochlear nerve preservation was achieved

In one of the above cases, a suspected VS was revealed as a facial nerve schwannoma (FNS) during surgery. As the tumour originated within the internal auditory canal, the symptomatology and many of the issues confronted during the excision (with regard to preservation of hearing) were similar to that of a VS. For this reason, the findings from the FNS case have also been reported and incorporated into the discussion.

Table 1. Summary of pre- and postoperative data for patients suffering anacusis following vestibular schwannoma surgery.

			Preoperative				**Postoperative**		
Case	*Age (yr)*	*Tumour size (mm)*	*PTA (dBHL)* *WRS (%)*	*DPOAEs*	*ABR I* *ABR V (ms)*	*Nerve Saved*	*PTA (dBHL)*	*DPOAEs*	*ABR I* *ABR V (ms)*
3.	43	35	75 dB HL* 10 %	Absent	NR NR	No	NR	Absent	NR
4.	49	28	90 dB HL 0 %	1-3 kHz	2.1 (I) NR	No	NR	Absent	NR
5.	61	32	50 dB HL 70 %	1-1.5 kHz	1.75 (I) 5.5 (III) 7.5 (V)	No	NR	Absent	NR
6.[FN]	51	20	100* 0 %	Absent	NR NR	No	NR	Absent	NR

NR = no recordable response, FN: Facial nerve schwannoma case

PTA = pure-tone average calculated from the patient's threshold at 0.5, 1 & 2 kHz

* No measurable hearing above 1 kHz (PTA: 0.5 & 1 kHz)

In the group who suffered permanent anacusis tumour size (according to maximal diameter) was large (>30 mm) in 2 patients and medium (15 - 29 mm) in 2 patients. All patients had type "A" tympanograms indicating normal middle ear pressure and compliance. Measurable hearing was documented during the preoperative assessment in all 4 cases. In addition, 2 patients demonstrated good cochlear function in the low to mid frequencies, confirmed by the presence of DPOAEs and wave I of the ABR. Latency of wave I in both cases was considered to be normal. Wave III and V of the ABR were also evident in one case preoperatively however the latency of these waves were abnormally prolonged at 5.5 ms and 7.5 ms respectively (Hood, 1998). None of the patients in this group demonstrated serviceable hearing according to the 50/50 rule prior to surgery.

Anatomic cochlear nerve preservation was not achieved in any of the patients suffering anacusis postoperatively. Following surgery, all patients had type "A" tympanograms indicating normal middle ear pressure and compliance. Measurable hearing could not be demonstrated in this group postoperatively. Likewise, no reproducible potentials could be obtained when recording the ABR. DPOAEs were absent in the 2 patients who demonstrated good cochlear function before the operation. Detailed results for each case of postoperative anacusis are presented in the appendix; section II.

3.2. Permanent hearing preservation

The remaining 2 patients who underwent surgery for removal of a VS experienced permanent hearing preservation. Pre- and postoperative findings for these patients are presented in detail. Table 2 displays a summary of the pre- and postoperative data for these patients including:

i) patient age
ii) tumour size
iii) pure-tone average (PTA)
iv) word recognition score (WRS)
v) presence or absence of DPOAEs
vi) ABR peak latencies, where available; and
vii) whether anatomic cochlear nerve preservation was achieved

Table 2. Summary of pre- and postoperative data for patients experiencing permanent hearing preservation following vestibular schwannoma surgery.

			Preoperative				**Postoperative**		
Case	*Age (yr)*	*Tumour size (mm)*	*PTA (dBHL) WRS (%)*	*DPOAEs*	*ABR I ABR V (ms)*	*Nerve Saved*	*PTA (dBHL) WRS (%)*	*DPOAEs*	*ABR I ABR V (ms)*
1.	29	11	25 dB HL 100 %	1-2 kHz	2.1 (I) 8.3 (V)	Yes	60 dB HL 64 %	1-2 kHz	2.1 (I) 7.2 (V)
2.	57	16	55 dB HL 91 %	Absent bilaterally	1.8 (I) NR	Yes	85 dB HL 0 %	Absent bilaterally	NR[†] NR

NR = no recordable response

PTA = pure-tone average calculated from the patient's threshold at 0.5, 1 & 2 kHz

[†] Wave I was initially documented at 2.0 ms but disappeared on postoperative day 7

3.2.1. Case 1

In August 2006 a 29-year-old male presented to his GP with tinnitus and a "blocked" feeling in the left ear. The patient reported suffering a knock to the head 3 years prior and a history of recreational noise exposure from rifle shooting. He was not suffering any vertigo or unsteadiness and was not taking any medications. Following referral to an Ear, Nose and Throat Surgeon and a subsequent MRI carried out at Christchurch Public Hospital the patient was diagnosed as having a small sized VS measuring 11 mm in maximal diameter.

In July of 2007 the patient was admitted to Christchurch Public Hospital for excision of unilateral VS. The findings of his preoperative audiological assessment are detailed in Figures 11 and 12. Tympanometry yielded type "A" tympanograms bilaterally, consistent with normal middle ear pressure and compliance. Pure tone audiometry indicated a mild to moderate sloping sensorineural hearing loss in the left ear (PTA of

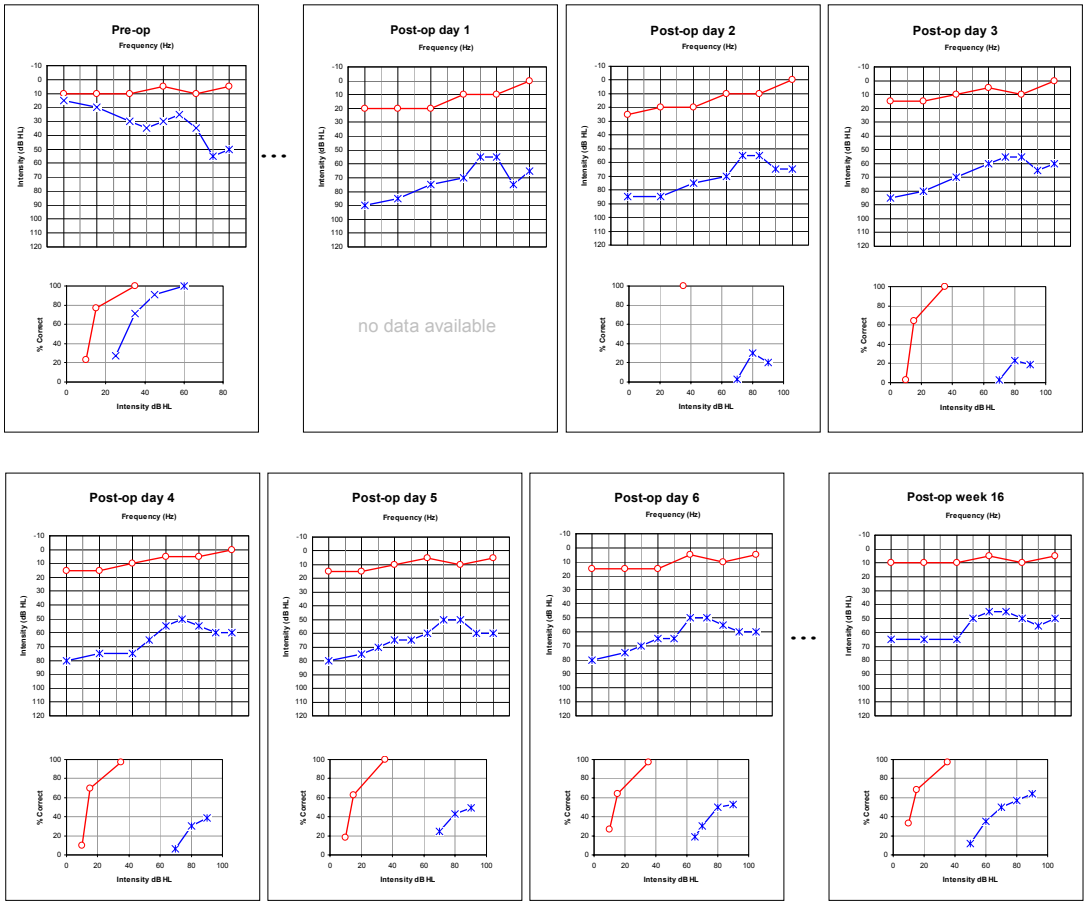
25 dB HL) and normal hearing in the right ear. This represented a significant asymmetry in hearing across the range of frequencies tested, particularly in the high frequencies. Speech audiometry showed speech discrimination was consistent with the pure tone audiogram. Specifically, the patient had a SRT of approximately 30 dB HL and a WRS of 100% when speech was presented to the left ear. Objective measures of cochlear function via DPOAEs indicated emissions were present from 1-6 kHz in the right ear and 1-2 kHz in the left ear. The ABR recorded from the right ear was normal in terms of waveform latency and morphology for waves I to V (Hood, 1998). The ABR recorded from the left ear showed a reproducible wave I (2.1ms) with a latency that was considered to be within the normal range (Hood, 1998). It should be noted however, that wave I was reduced in amplitude and of slightly prolonged latency compared to the right ear (1.75 ms). Wave V was also documented on the left side. It had an abnormally prolonged latency of 8.3 ms (IT5 of 2.2) but normal morphology.

Three hours after surgery, an ABR revealed a clear and reproducible wave I (2.1 ms) however no other waves were apparent. Tympanometry yielded type "A" tympanograms bilaterally. Pure tone audiometry conducted 24 hours following the operation indicated the patient had severe to moderately-severe rising sensorineural hearing loss in the left ear (PTA of 75 dB HL) and normal hearing in the right ear. Speech audiometry could not be preformed at this time as the patient was feeling unwell. On the second postoperative day speech audiometry revealed a WRS of 30% for words presented to the left side at 90 dB HL, significantly poorer than expected based on the audiogram. An ABR could not be recorded on postoperative day 2 as the

patient was unavailable for testing. During the remaining hospitalisation the patient demonstrated a small but gradual improvement in both pure-tone and speech audiometry for the left ear. On the final day in hospital (postoperative day 6) a PTA of 65 dB HL and WRS of 53% for words presented at 90 dB HL was documented. DPOAEs were present from 1 to 2 kHz on the left. No significant changes were evident in the right ear for any measure. During the postoperative course no change in the ABR was observed for either ear. For the left side, wave I latency remained stable and wave V was still absent on discharge.

In November 2007, 16 weeks after surgery, the patient was seen again for audiological assessment. At this time, a PTA of 60 dB HL and WRS of 64% for words presented to the left ear at 90 dB HL was documented; representing a small but clinically significant improvement. DPOAEs were present from 1 to 2 kHz on the left. Although there was no change in wave I of the ABR, a clear and reproducible wave V could be seen. The latency of this wave (7.2 ms) had reduced significantly compared to the preoperative response (8.3 ms). Again, there was no change on the right side for any measure. Although the patient demonstrated an improvement in hearing, it not considered serviceable. The findings of preoperative and postoperative audiological assessment of case 1 are presented in Figure 11 and 12. In Figure 11, the results of pure-tone and speech audiometry are shown in part A, DPOAEs in part B and part C shows changes in pure-tone thresholds over time. Figure 12 displays a time-ordered sequence of ABRs recorded from the patient before and after surgery.

A.



B.

Pre-op DPOAEs		f_2 (Hz)					
		1000	1500	2000	3000	4000	6000
SNR	*Right*	+	+	+	+	+	+
	Left	+	+	+	-	-	-

Post-op DPOAEs		f_2 (Hz)					
		1000	1500	2000	3000	4000	6000
SNR	*Right*	+	+	+	+	+	+
	Left	+	+	+	-	-	-

C.

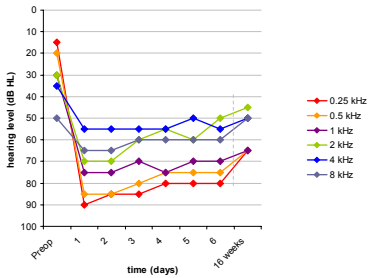


Figure 11. Case 1: audiological assessment before and after vestibular schwannoma surgery. Results of pure-tone and speech audiometry are shown in part A. The right and left ear are represented by circles and crosses respectively (filled circles and marked crosses indicate the use of contralateral masking). Part B shows the presence or absence of DPOAEs from 1 to 6 kHz and part C displays changes in pure-tone thresholds over time.

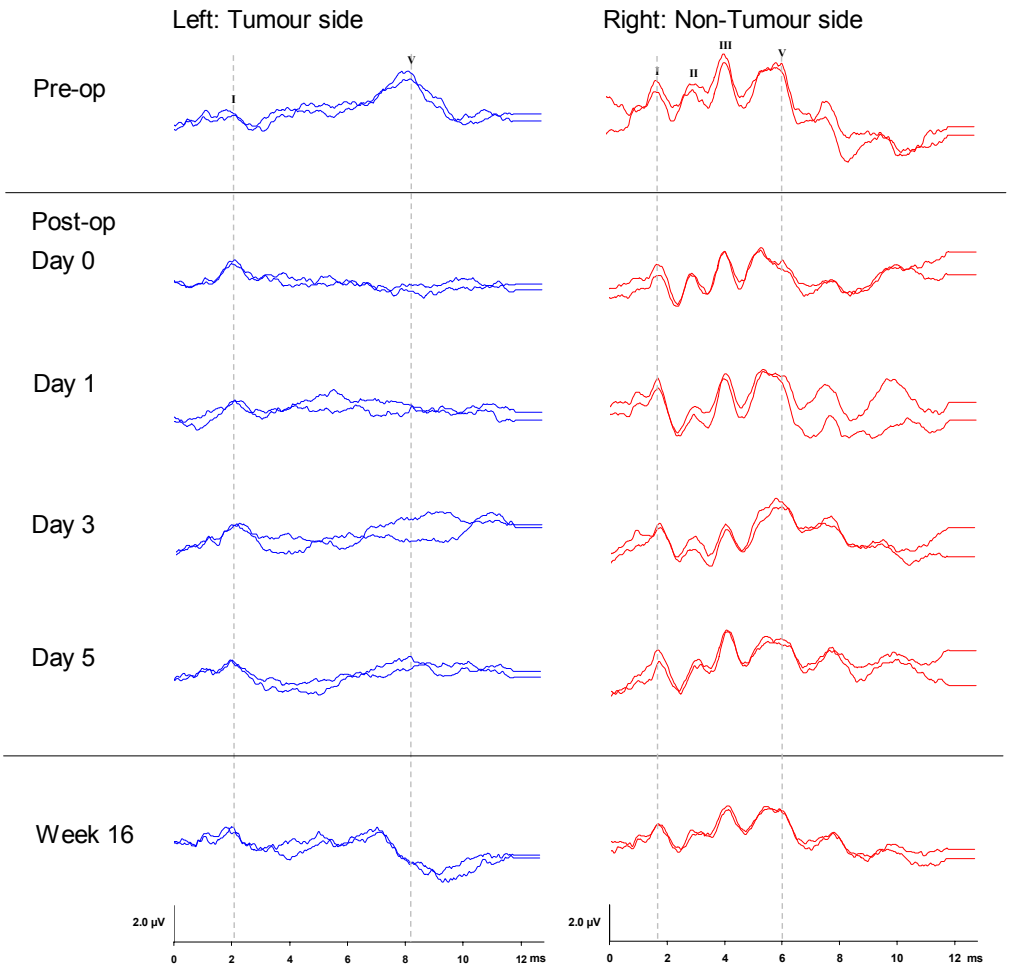


Figure 12. Case 1: time-ordered sequence of click evoked ABRs recorded before and after vestibular schwannoma surgery.

3.2.2. Case 2

In November 2006 a 57-year-old female presented to her GP with a “blocked” feeling in the right ear and several months later, ear pain on the same side. The patient reported suffering viral meningitis approximately 12 years prior and a history of hypertension which was being controlled with medication. The patient also reported taking Thyroxine. She was experiencing mild unsteadiness and low level unilateral tinnitus on the right side. Following referral to an Ear, Nose and Throat Surgeon and a subsequent MRI carried out at Christchurch Public Hospital the patient was diagnosed as having a medium sized VS measuring 16 mm in maximal diameter.

In July of 2007 the patient was admitted to Christchurch Public Hospital for excision of unilateral VS. The findings of her preoperative audiological assessment are detailed in Figure 13 and 14. Tympanometry yielded type "A" tympanograms bilaterally, consistent with normal middle ear pressure and compliance. Pure tone audiometry indicated a moderate U-shaped sensorineural hearing loss in the right ear (PTA of 55 dB HL) and a mild to moderate U-shaped sensorineural hearing loss in the left ear (PTA of 45 dB HL), which recovered to normal hearing in the high frequencies. This represented a significant asymmetry in hearing across the range of frequencies tested. Speech audiometry showed speech discrimination was consistent with the pure tone audiogram. Specifically, the patient had a SRT of approximately 50 dB HL and a WRS of 91% when speech was presented to the left ear at 70 dB HL. When performance was assessed at higher intensities, the rollover effect was evident.

Objective measures of cochlear function via DPOAEs indicated emissions were absent bilaterally. The ABR recorded from the left ear was normal in terms of waveform latency and morphology for waves I to V (Hood, 1998). The ABR recorded from the right ear showed a reproducible wave I (1.8 ms) with a latency that was considered to be within the normative range (Hood, 1998). It should be noted however, that wave I was of slightly prolonged latency compared to the left ear (2.0 ms). There was no evidence of wave V.

Three hours after surgery, an ABR on the right revealed a clear and reproducible wave I (2.1 ms). No other waves were apparent. Tympanometry yielded type "A" tympanograms bilaterally. Pure tone audiometry conducted 24 hours following the operation indicated the right ear had a moderately-severe to severe sloping sensorineural hearing loss in the low frequencies with no measurable hearing at 1 kHz or above. Speech audiometry showed a WRS of 0% for words presented to the right side at 80 and 90 dB HL, significantly poorer than expected based on the audiogram. No significant change in the ABR, pure-tone or speech audiometry was documented in the left ear.

During the remaining hospitalisation the patient demonstrated a small but gradual improvement in pure-tone audiometry for the right ear. On postoperative day 2, the patient regained at least 30 dB of hearing at 1 and 1.5 kHz. Hearing at 2 kHz became measurable on postoperative day 6. On the final day in hospital (postoperative day 6) a PTA of 85 dB HL and WRS of 0% for words presented at 80 and 90 dB HL was

documented. DPOAEs were absent bilaterally. No significant changes were evident in the left ear for any measure. Following surgery progressive changes in the ABR were observed for the right ear. In particular, wave I latency gradually became prolonged following postoperative day 2. Although waveform morphology on day 5 was reasonably normal, by postoperative day 6, wave I had broadened significantly. On the patient's final day in hospital (day 7) wave I was absent. Waveform morphology and latencies on the left remained stable throughout hospitalisation.

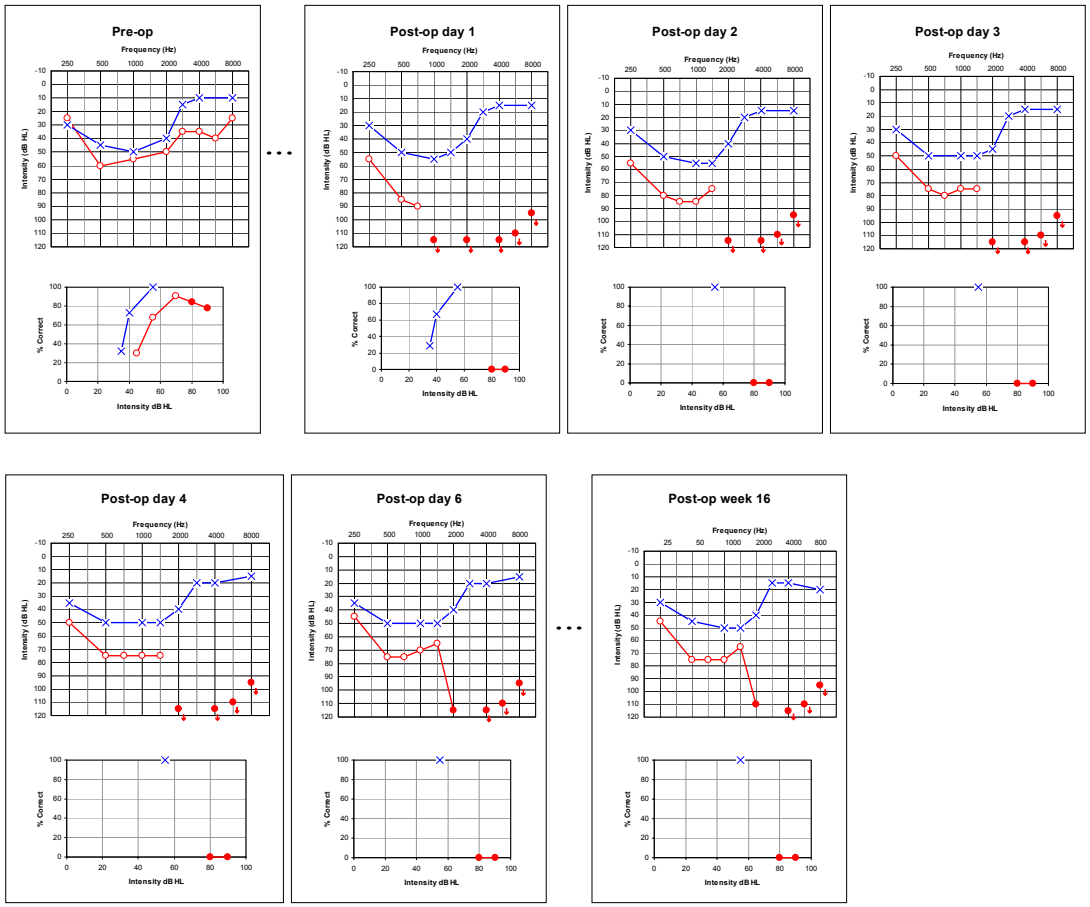
In November 2007, 16 weeks after surgery, the patient was seen again for audiological assessment. At this time, a PTA of 85 dB HL and WRS of 0% for words presented to the right ear at 80 and 90 dB HL was documented. DPOAEs were absent bilaterally. To determine the level of cochlear function, an ECochG was performed during this assessment. Transtympanic recordings taken from the right ear confirmed the marked reduction of the CAP, but a large CM and SP were present. Table 3 shows the amplitude values for the CAP, CM and SP for click stimuli and tone bursts at 1 kHz and 4 kHz presented to each ear individually. Based on these findings, this patient was considered to have retained cochlear function. However, due to poor neural function, hearing was not considered serviceable on the right side. The findings of preoperative and postoperative audiological assessment of case 2 are presented in Figure 13 and 14. In Figure 13, the results of pure-tone and speech audiometry are shown in part A, DPOAEs in part B and part C shows changes in pure-tone thresholds over time. Figure 14 displays a time-ordered sequence of ABRs recorded from the patient before and

after surgery. Also included in Figure 14 are the electrocochleograms evoked by 4 kHz tone burst that were recorded 16 weeks following surgery.

Table 3. Amplitude values for the compound action potential (CAP), cochlear microphonic (CM) and summating potential (SP) for click stimuli and tone bursts at 1 kHz and 4 kHz presented to each ear individually.

	Left: non-operated side			**Right: operated side**		
Stimuli	CAP (μV)	SP (μV)	CM (μV)	CAP (μV)	SP (μV)	CM (μV)
Click	-45.7	-9.9	n/a	-16.9	-10.8	n/a
1 kHz	-7.0	-1.2	17.1	-3.8	-3.6	18.4
4 kHz	-14.4	-1.6	18.5	-7.1	-7.0	27.7

A.



B.

Pre-op DPOAEs		f_2 (Hz)					
		1000	1500	2000	3000	4000	6000
SNR	*Right*	-	-	-	-	-	-
	Left	-	-	-	-	-	-

Post-op DPOAEs		f_2 (Hz)					
		1000	1500	2000	3000	4000	6000
SNR	*Right*	-	-	-	-	-	-
	Left	-	-	-	-	-	-

C.

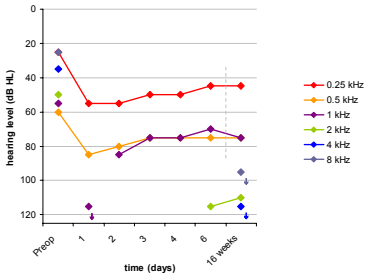


Figure 13. Case 2: audiological assessment before and after vestibular schwannoma surgery. Results of pure-tone and speech audiometry are shown in part A. The right and left ear are represented by circles and crosses respectively (filled circles and marked crosses indicate the use of contralateral masking). Part B shows the presence or absence of DPOAEs from 1 to 6 kHz and part C displays changes in pure-tone thresholds over time.

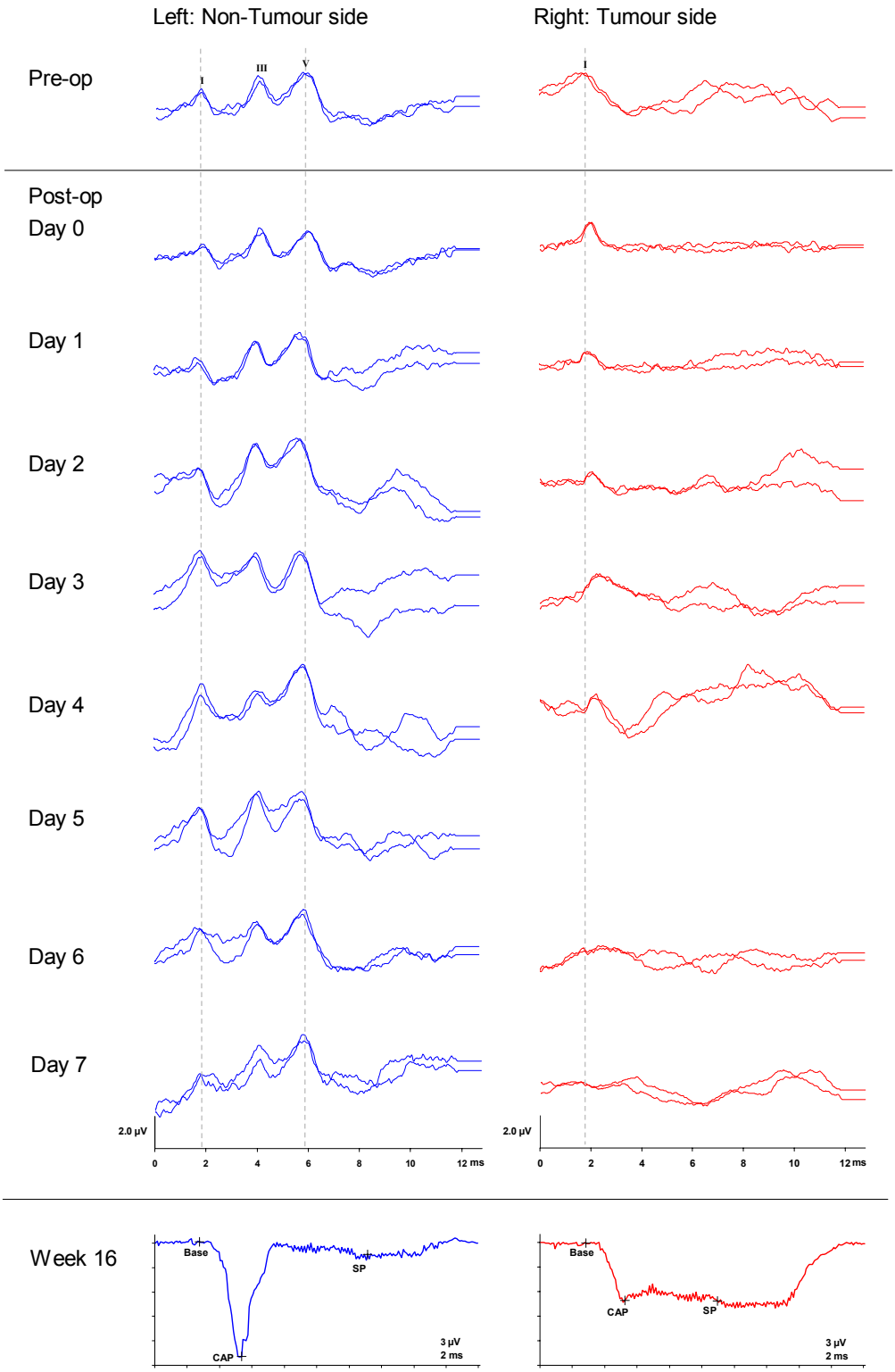


Figure 14. Case 2: Time-ordered sequence of click evoked ABRs recorded before and after vestibular schwannoma surgery. Lower traces: transtympanic electrocochleograms evoked by 4 kHz tone burst recorded from the left and right ears 16 weeks after surgery.

4. DISCUSSION

In an effort to detect and define the phenomenon of delayed hearing loss, the current study closely monitored electrophysiological and behavioural responses in patients following vestibular schwannoma (VS) surgery. In particular, it was hoped that by confirming the site of impairment, the mechanism leading to delayed loss could be established and thus avoided in the future. From a series of a 6 consecutive patients who underwent surgery for unilateral VS, postoperative monitoring revealed that 4 patients suffered permanent anacusis and the remaining 2 patients had permanent hearing preservation. During the time period available for this thesis, there were no patients who experienced delayed hearing loss in the early postoperative period. Such a finding was not entirely unexpected considering how seldom this phenomenon has been documented in the literature (Fahlbusch, Neu, & Strauss, 1998; Neu, Strauss, Romstock, Bischoff, & Fahlbusch, 1999; Palva, Troupp, & Jauhiainen, 1985; Strauss et al., 1991).

Due to the variation in design and inclusion criteria of these studies, it is difficult to establish what proportion of cases can be expected to suffer from delayed hearing loss. Neu et al. (1999) published the largest study so far that has concentrated on postoperative hearing fluctuation. They reported that 11 out of the 70 patients in their study suffered delayed hearing loss, representing approximately 16% of all cases. It is important to note, however, that patient inclusion criteria for their study required measurable hearing and reproducible wave I and/or V of the ABR preoperatively (Neu,

Strauss, Romstock, Bischoff, & Fahlbusch, 1999). In the current study, all patients who underwent surgery for excision of unilateral VS were included regardless of preoperative auditory function. If the inclusion criteria employed by Neu et al. (1999) were applied to our study, only 4 out of a total of 6 patients would have been monitored postoperatively. Based on an incidence of 16%, the chance of observing delayed hearing loss in a group of this size is considered unlikely.

In addition to patient inclusion criteria, other factors may influence the incidence of delayed hearing loss. In particular, the surgeon's technique and operative approach during the VS excision may have an effect on postoperative pathophysiology. For this reason, the likelihood of provoking the mechanism that leads to delayed hearing loss may have been lower in the current study compared with previous studies. However, reports of early postoperative hearing deterioration following VS excision have been made by surgeons at Christchurch Hospital (P. Bird, personal communication, November 19, 2006). Thus, although there is an indication that this phenomenon has occurred in the past, the proportion of patients who were affected was not documented.

4.1. Preoperative findings

It is unlikely that preoperative factors, such as tumour size, influenced the proportion of patients suffering delayed hearing loss in the current study. The average tumour size in this study measured 24 mm, very similar to that reported in the Neu et al. (1999) study in which 11 of 70 cases experienced delayed hearing loss. In terms of international norms, however, recent large-scale research on referral patterns of patients with VS

have reported considerably smaller mean tumour sizes, ranging from 10 to 16 mm (Chen, 2007; Stangerup et al., 2004; Tos, Stangerup, Caye-Thomasen, Tos, & Thomsen, 2004). As with the present study, tumour size was measured according to its maximal extrameatal diameter. The fact that average tumour size was found to be larger in the present study indicates that a longer time period may have elapsed between initial symptoms and diagnosis of VS. A timely diagnosis is critical because identifying the tumour while it is small means there is a lower risk of morbidity and higher chance of hearing preservation following excision (Kanzaki, Ogawa, Inoue, Shiobara, & Toya, 1998). Why diagnosis was delayed in our patients is not clear. Symptom awareness and education of local sources of referral may need to be improved, although these issues are beyond the scope of this thesis and necessitate further investigation.

Despite a larger mean tumour size, measurable hearing was documented in all patients prior to surgery. However, according to the Nordstadt classification scheme used in a large study by Samii & Matthies (1997), 2 out of 6 patients in our study were considered to have no *functional* hearing preoperatively. Similarly, Samii & Matthies (1997) reported that 27% of their cases were found to be functionally deaf before surgery. In agreement with Harner et al. (2000), overall hearing loss in our patients tended to be more substantial in the high frequencies. Pure-tone thresholds and word recognition ability was generally poorer than documented in other studies (Harner, Fabry, & Beatty, 2000) which may be related to the larger mean tumour size observed in the current study. Indeed, the single case that presented with serviceable hearing preoperatively (PTA < 50 dB HL and WRS > 50%) also had the smallest tumour size.

Nadol, Diamond, & Thornton (1996) reported a statistically significant correlation between the largest tumour diameter and the severity of low-frequency sensorineural hearing loss. It should be noted, however, that most authors generally report little correlation between preoperative audiometric parameters and tumour size (Harner, Fabry, & Beatty, 2000; Stipkovits, van Dijk, & Graamans, 1998). This finding is supported by the fact that case 5, who presented with borderline serviceable hearing and reproducible ABR waves I, III and V, had one of the largest tumours.

Although the mechanism of the hearing loss associated with VS growth remains unclear, both cochlear and retrocochlear impairment are commonly observed in these patients preoperatively (O-Uchi et al., 1994). In the current study, only two cases had a reproducible wave V before surgery. In both of these cases latency was significantly prolonged and morphology was unusual, providing evidence of poor neural function. This finding can be related to delays in neural activation and poorer overall synchronicity of the response due to compression of the cochlear nerve by the tumour. Matsunaga and Kanzaki (2000) examined microvessels and nerve fibres in the intracanalicular portion of the eighth nerve in patients with unoperated VS. Their findings were consistent with a slight to moderate reduction of endoneurial blood flow in the eighth nerves of these individuals (Matsunaga & Kanzaki, 2000). As noted earlier, retrocochlear impairment in patients with VSs is reported in the majority of cases (Telischi, 2000). The complete absence of wave V likely represents a more severe case of neural compression where synchronicity is severely disrupted or too few fibres are left to generate a gross potential that can be detected (Hall, 2006). Alternatively,

absence of wave V may be the result of a total neuronal conduction block. However, at least some neural function was demonstrated behaviourally in two of the cases with an absent wave V, indicating temporal dispersion without conduction block. The remaining two cases had no behavioural responses above 1 kHz. Although this finding may indicate a neuronal conduction block in the high frequencies, the absence of wave I and DPOAEs suggests cochlear dysfunction was also present.

Cochlear dysfunction in unoperated VS cases has been reported previously by a number of authors (Gouveris, Victor, & Mann, 2007; Mahmud, Khan, & Nadol, 2003; Prasher, Tun, Brookes, & Luxon, 1995; Yokoyama, Nishida, Noguchi, & Komatsuzaki, 1999). All patients in this study exhibited lower DPOAE amplitudes on the tumour side compared to the non-tumour side, with the exception of case 2 where emissions were absent bilaterally (due to a pre-existing sensorineural hearing loss). In the other individuals, emission strength on the tumour side tended to be lower across all frequencies (1-6 kHz) and was often absent in the high frequencies. Noguchi et al. (1998) observed that hearing loss in the high tone range appeared to be induced by cochlear dysfunction. Similar findings were reported by Telischi (2000). The absence of DPOAEs suggests damage to the cochlea and in particular the OHCs, which are extremely sensitive to ischemia. A tendency for impairment of the OHCs located in the more basal high frequency region of the cochlea is consistent with reports that in animals, this region is most sensitive to vascular occlusion (Kimura, 1986).

In addition to OHC damage, histopathological findings in cases of unoperated VS have shown degeneration of IHCs, stria vascularis and the spiral ligament (Mahmud, Khan, & Nadol, 2003). In the current study, possible evidence of IHC impairment was observed in several cases. Specifically, in case 1 and 2 wave I latency recorded from the lesion side was significantly prolonged compared to the non-lesion side. Although ABR waveforms are relatively immune to effects of cochlear hearing loss at high intensity levels, audiometric configuration has been shown to influence ABR absolute latencies (Gorga, Worthington, Reiland, Beauchaine, & Goldgar, 1985; Keith & Greville, 1987; Watson, 1996). In the case of high frequency and notched hearing losses, wave I latency is systematically prolonged with increasing levels of cochlear impairment (Watson, 1996). Studies have indicated that wave I generation to high level clicks represent the synchronized response of a large proportion of the cochlear basal turn (Hall, 2006). If the number of functional IHCs within this region were reduced, wave I of the ABR would reflect the response from a more apically activated region of the cochlea where IHCs were still intact. Consequently, travel time along the basilar membrane would be longer and thus, result in prolonged wave I latency (as seen in case 1 and 2). Alternatively, asymmetric wave I latency may be a result of impaired neural conduction or poor synaptic efficiency in the peripheral portion of the nerve on the lesion side. Impairment of the OHCs was probably not responsible for affecting wave I latency in this study as the contribution from the active process is negligible at high stimulus intensities (Dallos, 1992).

Assessing OAEs in patients with unoperated VS not only provides valuable information regarding cochlear function, this measure can also (by exclusion) provide evidence of impaired neural function. In one patient (case 4) DPOAEs were present from 1 to 3 kHz despite pure-tone audiometry indicating a severe to profound hearing loss at the same frequencies. In another patient (case 5), DPOAEs at 1 to 1.5 kHz were clearly present although the patient had a 1 kHz pure-tone threshold of 50 dB HL. Because emissions cannot normally be recorded when cochlear hearing loss exceeds 40 dB HL (Gorga, Neely, & Dorn, 1999), these observations indicate retrocochlear pathology was responsible for the audiometric hearing loss. Evidence of relatively good cochlear function, but poor neural function was further supported by normal wave I latency and an absent wave V. Prasher et al. (1995) reported that TEOAEs were present in 7 of 26 patients with VS when pure-tone averages were lower than 40 dB HL.

4.2. Postoperative anacusis

Four out of a total of 6 patients (66.7%) suffered permanent anacusis postoperatively. All patients had measurable hearing preoperatively, although none of this group demonstrated serviceable hearing according to the 50/50 rule. A similar outcome was reported in large study published by Sammii & Matthies (1997), who found that 60.5% of cases who had hearing preoperatively did not have a functional cochlear nerve following the operation. Progressively lower values of postoperative hearing preservation have been reported as tumour size increases (Gjuric, Mitrecic, Greess, & Berg, 2007; Hecht, Honrubia, Wiet, & Sims, 1997; Matthies & Samii, 2002; Samii & Matthies, 1995). This is especially the case for patients with large tumours (>30 mm),

for whom preservation of hearing is considered by some to be unrealistic (Frerebeau et al., 1987; Hecht, Honrubia, Wiet, & Sims, 1997; Patuzzi, Yates, & Johnstone, 1989). In the current study, 2 patients who suffered anacusis postoperatively had large tumours. The other 2 patients had medium sized tumours.

It has been postulated that larger tumours tend to extend further into the IAC, thus raising intracanalicular pressure (Lapsiwala, Pyle, Kaemmerle, Sasse, & Badie, 2002). The pressure on the cochlear nerve and on vascular structures may increase the vulnerability of the already compromised nerve within the IAC during surgical drilling and nerve manipulation (Mohr, Sade, Dufour, & Rappaport, 2005). Additional elevation of intracanalicular pressure during surgery may lead to spasm or obstruction of blood flow to the cochlea, decreasing the likelihood of postoperative hearing preservation. It has also been suggested that patients with smaller tumours are more likely to have a cochlear nerve which is morphologically intact, making it easier to identify and therefore preserve (Umezu & Aiba, 1994). As the tumour enlarges, the cochlear nerve is compressed and more of the nerve may be invaded by tumour cells, distorting its morphology (Matsunaga, Kanzaki, & Igarashi, 1995). Severe cochlear nerve invasion by VS tumour cells resulting in fibrosis and nerve degeneration has been reported (Matsunaga & Kanzaki, 1996). Under such circumstances, complete tumour excision often requires considerable nerve manipulation, increasing the risk of damage to the nerve itself and surrounding vascular structures. Moriyama et al. (2002) reported that the presence of severe adhesion in the interface between the cochlear nerve and the tumour is possibly the most significant prognostic factor for hearing preservation. In

the current study, anatomic cochlear nerve preservation was not achieved in any of the patients suffering anacusis postoperatively.

It is interesting to note that the two patients with preoperative cochlear function who suffered anacusis both lost DPOAEs and wave I of the ABR following VS excision. This observation indicates that, in addition to nerve severance, damage to the cochlea was also sustained during surgery. Morawski et al. (2004), who monitored DPOAEs intraoperatively during VS excision, reported that bipolar cautery close to the IAC structures had the greatest impact on emissions. Telischi et al (1995) and Cane et al. (1992) both reported on cases where OAEs were permanently lost following dissection of the tumour from the eighth nerve. Other authors have noted that severance of the eighth nerve fibres with complete sparing of the IAA is extremely difficult (Shimamura, Sekiya, Yagihashi, & Suzuki, 2002). According to Sekiya et al. (1985) disappearance of wave I during manipulation the eighth cranial nerve always results from such vascular compromise. Thus, damage to cochlear structures in the current study was most likely the result of a transient interruption in blood supply due to vasospasm or embolism of the IAA. Whether residual cochlear function was lost in the 2 remaining cases of postoperative anacusis cannot be determined, as DPOAEs and ABR wave I were absent preoperatively.

In addition to tumour size, preoperative hearing (PTA and WRS) correlates well with hearing preservation rates (Brackmann et al., 2000; Robinette, Bauch, Olsen, Harner, & Beatty, 1997). Indeed, having preoperative serviceable hearing is considered by many

surgeons as a criterion to attempt hearing preservation (Kaylie, Gilbert, Horgan, Delashaw, & McMenomey, 2001). Although Josey et al. (1988) reported that good hearing was not necessarily a good predictor of successful hearing preservation, they found poor speech discrimination accurately indicated failure. In the current study, those patients who suffered anacusis postoperatively tended to have worse preoperative hearing, particularly when compared to the non-lesion side. The association between pre- and postoperative hearing function is not surprising given that hearing thresholds rarely improve after VS excision. Indeed, the vast majority of cases have been shown to experience a decline in thresholds following hearing preservation surgery (Harner, Fabry, & Beatty, 2000). Preoperative word recognition in these patients was also generally poorer than predicted based on the audiogram. This suggests that although there was signal transmission along the peripheral auditory pathway, nerve impulses were sufficiently desynchronized to make word recognition difficult.

Poor neural synchrony was also indicated by an absence of wave V in 3 out of 4 cases suffering anacusis in the current study. A number of authors have reported that preoperative ABR morphology correlates well with hearing outcome (Brackmann et al., 2000; Josey, Glasscock, & Jackson, 1988; Moffat, da Cruz, Baguley, Beynon, & Hardy, 1999; Robinette, Bauch, Olsen, Harner, & Beatty, 1997). It has been proposed that this correlation exists because the ABR reflects physiological integrity of the cochlear nerve fibres (Moffat, da Cruz, Baguley, Beynon, & Hardy, 1999). In particular, poor ABR morphology may indicate tumour infiltration of the cochlear nerve, resulting in irreversible loss of neural fibres and thus poor neural synchrony. As noted previously,

VS excision in cases where the tumour is invasive often requires more nerve manipulation, increasing the risk of injury to auditory structures. In contrast, prolonged wave V latency but preserved waveform morphology may reflect an interruption to nerve conduction due to pressure exerted by the tumour (rather than nerve invasion). In this situation, removal of the tumour is likely to require less surgical manipulation and therefore have a better outcome in terms of hearing preservation.

It is important to note that absent ABR potentials do not contraindicate attempted hearing preservation. A study conducted by Roberson, Jackson, & McAuley (1999) reported that hearing preservation was achieved in 7 out of 9 patients with an absent preoperative ABR. Furthermore, an improvement in hearing class following surgery was documented in 4 of these patients. In the current study, the 2 patients with absent ABR potentials preoperatively (case 3 and 6) both suffered anacusis. A possible explanation for this disparity relates to the origin of the preoperative hearing impairment. In cases where VS hearing loss is principally neural in origin, surgery may provide a reversal of pressure caused by the tumour, resulting in an improvement in neural conduction. Whereas hearing loss resulting from vascular occlusion that is predominantly cochlear in origin is more likely to be permanent and therefore will not recover following tumour removal. In support of this theory, the absence of DPOAEs (on the operated side only) in case 3 and 6 of the current study provide evidence of preoperative cochlear impairment associated with anacusis following surgery. Furthermore, Kim, Edwards, Telian, Kileny, & Arts (2006) reported that good cochlear function, indicated by robust preoperative TEOAEs, is a favourable prognostic

indicator for hearing preservation following VS surgery. The study by Roberson et al. (1999) did not provide any evidence concerning cochlear function in their patients. In future studies, it may be useful to measure cochlear function in cases of hearing loss caused by VS to better differentiate vascular from neural compression.

4.3. Postoperative hearing preservation

In the current study, 2 out of a total of 6 patients experienced permanent hearing preservation following surgery. Both patients had measurable hearing preoperatively, although only one case demonstrated serviceable hearing according to the 50/50 rule. In agreement with Harner et al. (2000), auditory function following surgery was worse in both cases, with neither patient demonstrating serviceable hearing up to 3 months after surgery. Specifically, drops in the PTA of 35 dB and 30 dB were documented in cases 1 and 2 respectively. Nadol et al. (1992) reported that 85% of their cases experienced at least a 15 dB deterioration in hearing level. Likewise, Samii and Matthies (1997) reported that following surgery 85% of patients were downgraded by at least 1 hearing classification grade (corresponding to a 30 dB deterioration). Thus, although hearing is often reported as “preserved”, this term can be misleading as the vast majority of patients suffer a significant hearing loss following VS surgery. Furthermore, reporting hearing as “preserved” provides little indication of its usefulness to the patient.

As mentioned previously, rates of hearing preservation reported in the literature vary widely. This variation is in part due to differing definitions on what constitutes preserved hearing. Some authors consider any measurable hearing as preserved hearing,

while others consider only serviceable hearing as preserved hearing. Magnan et al. (2002) demonstrated how choosing different reporting criteria affected their own hearing preservation rates, which were 49% for measurable hearing and 30% for serviceable hearing. Patient selection criteria can also dramatically influence hearing preservation rates. The high overall rate of hearing preservation reported by Magnan et al (2002) may in part be due to the fact that only patients with a tumour size of less than 25 mm were included in their study. In contrast, Samii and Matthies (1997) included all VS cases that presented between 1978 and 1993 and demonstrated overall preservation rates of 30% and 15% for functional and serviceable hearing respectively. It should be noted however, that 289 cases were considered functionally deaf prior to surgery. Out of the 732 cases with preoperative hearing, preservation rates were 40% for functional hearing and 21% for serviceable hearing. Likewise, Lassaletta et al. (2003) reported that out of 33 cases with preoperative measurable hearing, 39% of their cases had measurable hearing postoperatively while only 15% demonstrated serviceable hearing. These results are in general agreement with the findings of the current study; indicating the actual probability of success in terms of preserving serviceable hearing following VS surgery is small. Even so, the retrosigmoid approach is a reliable surgical procedure for most VS tumours, offering the chance for hearing preservation with minimal morbidity and mortality.

In contrast to cases of postoperative anacusis, the aetiology of hearing impairment as a result of VS excision in cases 1 and 2 was probably not cochlear in origin. Depending on severity of injury, cochlear dysfunction can cause delay, attenuation or

disappearance of wave I (Legatt, 2002) and attenuation of DPOAEs. Although both cases suffered significant hearing loss during VS excision, little or no change in wave I morphology or latency was observed when comparing pre- and postoperative responses. Specifically, case 1 demonstrated no change in ABR wave I with a latency of 2.1 ms being recorded both before and after surgery. In addition, there were no changes to DPOAEs detected in this case. Indeed, evidence of impaired neural function in case 1 was indicated by the presence of DPOAEs from 1 to 2 kHz, despite pure-tone audiometry indicating a moderately severe hearing loss at these frequencies. In case 2, a small but significant prolongation of wave I was evident. However, the latency difference of 0.2 ms between pre and postoperative recordings does not account for the dramatic high frequency hearing loss observed in this case (Watson, 1996). Instead, mechanical damage to the proximal portion of the cochlear nerve was most likely sustained during surgical manipulation.

Direct nerve damage may have occurred at the operative site due to manipulation, compression and/or stretching during VS removal. The central portion of the cochlear nerve is particularly sensitive to direct damage, especially at the Obersteiner-Redlich (OR) zone. In this zone, the myelin sheath is less compact than in the peripheral portion where it is reinforced by collagen (Berthold, Carlstedt, & Corneliuson, 1993). In addition, the vascular system of the central portion is more sparsely and irregularly distributed compared to the peripheral nerve (Matsunaga, Kanzaki, & Hosoda, 1996). Sekiya & colleagues (1987; 1986) demonstrated that retraction of the eighth nerve in

dogs caused a disintegration of the myelin sheath, multiple foci of petechial hemorrhage and thromboses of the blood vessels supplying the cochlear nerve.

The profound high frequency neural impairment observed in case 2 is not surprising given the tonotopic arrangement of neural fibres within the cochlear nerve. Cochlear nerve fibres arising from the basal turn are situated more superficially (Sando, 1965) and therefore may be more prone to injury during VS surgery. This theory is supported by histological findings that show preservation of cochlear nerve fibres in the centre of the nerve trunk following static compression of the cochlear nerve in dogs (Hatayama, Sekiya, Suzuki, & Iwabuchi, 1999). In contrast, auditory function following VS surgery in case 1 was *poorer* in the low frequencies with less impairment evident at progressively higher frequencies. In fact, pure-tone audiometry in this patient indicated that there was no significant change between pre and postoperative thresholds above 4 kHz. The low frequency postoperative hearing impairment observed in case 1 is somewhat surprising and more difficult to explain. It is possible that the specific nerve fibres affected during tumour removal are dependent on the location of the tumour. In case 1, the tumour was found to arise from the inferior vestibular nerve. Although low frequency fibres from the apical turn of the cochlea are located in the medial portion of the cochlear nerve, they are directly adjacent to the inferior vestibular nerve (Spoendlin & Schrott, 1989). Thus, excision of a tumour arising from this nerve presents greater risk of injury to low-frequency fibres; particularly if adhesion between the cochlear nerve and tumour has occurred. No examples of a low frequency neural hearing loss caused by VS surgery could be found in the literature, although specific audiometric

findings are rarely described or explained. This is unfortunate, as detailed analysis of auditory function is crucial for establishing the likely mechanism of auditory impairment during VS surgery.

4.4. Auditory function improvement during the postoperative period

As highlighted in the present study, improvement in auditory function during the postoperative period is another factor that could affect reported hearing preservation rates. In both cases where hearing was preserved, patients demonstrated a small but gradual improvement in behavioural measures. Improvement was evident both during hospitalisation and at assessment 16 weeks postoperatively. This recovery was most notable in case 1, whose postoperative ABR findings showed a dramatic improvement at 16 weeks following surgery. In particular, wave V of the ABR which was initially documented preoperatively at 8.2 ms, disappeared completely following surgery and did not return during the remaining period of hospitalisation. At the follow-up assessment 16 weeks later, however, a clear and reproducible small wave V was recorded with a latency of 7.2 ms.

Postoperative changes in behavioural measures recorded from the operated side in both cases were also considered significant. Case 1 demonstrated an improvement in PTA of 15 dB and an increase in WRS from 30% to 64%. In addition, case 1 reported a gradual improvement in the self-perceived ability to differentiate pitch during pure-tone testing in the days following surgery (Case 1, personal communication, July 25, 2007). Results from case 2 are harder to analyse because initially this patient did not have any

measurable hearing above 750 Hz and lost all speech recognition ability following surgery. This had improved by the final day in hospital, with case 2 demonstrating measurable hearing up to 2 kHz, although this patient's WRS remained at 0%. Whether this represents a significant improvement in auditory function is debatable. No significant changes in PTA, SRT, WRS or ABR were observed in the unoperated ear for either case 1 or 2. This provides evidence that actual changes in auditory function did occur on the operated side in both cases. It should be noted, however, that on the first few days following surgery the PTA measured from the unoperated side of both patients was 5 dB higher than it was preoperatively. Rather than an actual worsening of the pure-tone threshold, this non-significant finding more likely provides an indication of the patient's reduced ability to participate in behavioural testing so soon after surgery.

An improvement in ABR findings during the postoperative period following VS surgery has been discussed in only a limited number of articles (Aoyagi et al., 1994; Hoehmann, 1991; Kveton, 1990). In the majority of cases, ABR latency gradually improved and became normal by 12 months after surgery. Tucci et al. (1994) reported that 10 of 17 cases with preserved hearing experienced improvements in ABR peak latency at long term follow-up, compared with preoperative findings. In terms of behavioural responses, the study by Tucci et al. (1994) demonstrated an average improvement in PTA of 6 dB between early and long term postoperative test results.

Gradual recovery in neural-auditory function following surgery may reflect the regenerative capacity of the eighth cranial nerve; part of the peripheral nervous system. Following loss of axonal continuity, injured axons in the peripheral nervous system are capable of resprouting long distances and have the ability to re-establish a functional link with their original targets. In humans, regeneration proceeds at approximately 2 mm per day (Recknor & Mallapragada, 2006). Over time, the capacity of the nerve to sprout axons may make it possible for individual cochlear neurons to successfully transverse an injury sustained during surgical manipulation. Several authors have demonstrated the robust and precise regeneration of the surgically sectioned eighth cranial in non-mammalian vertebrates (Newman & Honrubia, 1992; Zakon & Capranica, 1981). Eighth nerve regeneration in mammals is reported less often (Van De Water, Staecker, Ernfors, & Lefebvre, 1996). Although mammals appear to be capable of cochlear nerve resprouting, regrowth is usually limited in scope and disorganized (Spoendlin & Suter, 1976). Alternatively, injury to the cochlear nerve sustained during surgery may have been relatively mild, causing no axonal damage. In this case, a temporary conduction block can still occur despite preservation of axonal continuity. This type of nerve injury, known as neuropraxia, is most likely due to focal demyelination (Sunderland, 1951). As demonstrated by Hatayama et al. (1999), the cochlear nerve has the ability to recover from neuropraxia within weeks to months following compression injury. Thus, regeneration or recovery of the cochlear nerve remains a plausible explanation for the slow improvement in auditory function observed during the postoperative period in the current study. This is particularly true

for case 1 where significant recovery in wave V latency and speech recognition ability indicated improved neural function over time.

The comparison of pre- and postoperative measures for case 1 showed that wave V latency was ultimately shorter following the operation while behavioural thresholds were worse. This finding indicates that although neural conduction times ultimately became faster, following the operation there were fewer functional nerve fibres able to respond in a synchronous manner (that is, there was temporal dispersion). Wave V amplitude was also smaller after VS excision, providing further evidence of the limited number of responding neurons. In agreement with Spoendlin & Suter (1976), this finding suggests that the regenerative capacity of the cochlear nerve in this case was limited and did not completely overcome the damage sustained during surgery. However, although wave V latency was not yet normal at 16 weeks after surgery, it can be expected that neural recovery will continue to take place for up to 1 year (Aoyagi et al., 1994). The fact that hearing may continue to improve for many months following VS surgery should be taken into consideration when analysing and reporting rates of hearing preservation.

4.5. Case 2

4.5.1. Mechanism leading to loss of ABR wave I

Although case 2 also experienced limited improvement in behavioural thresholds during the early postoperative period, it was not reflected electrophysiologically. This is not surprising given that the ABR elicited by clicks is largely dependent on hearing

status in the frequency region of 2 to 4 kHz. In this case, the patient did not have any measurable hearing above 2 kHz. What is surprising, however, was the loss of wave I of the ABR on the 7th postoperative day despite its initial preservation. As noted above, the fact that case 2 demonstrated initial preservation of wave I following VS excision, yet had no measurable hearing above 2 kHz suggests that the hearing impairment sustained during surgery was at least neural in origin. In particular, preservation of wave I indicates that trauma to the cochlear nerve occurred centrally, at or near the operative site. This primary disturbance most likely caused a traumatic nerve block that specifically affected nerve fibres carrying high frequency information (above 2 kHz) from the cochlea. Whether this central impairment was due to microvascular disturbance or direct severance of neural fibres is not known. The loss of wave I of the ABR 7 days following surgery indicates that damage to the peripheral portion of the cochlear nerve and/or cochlea ultimately transpired. Although not demonstrated behaviourally, this phenomenon is very similar to that described by Strauss and colleagues (1991) in patients with delayed hearing loss. As with delayed hearing loss, the deterioration of wave I long after surgical manipulation had ended suggests a pathophysiological mechanism initiated during surgery that continues postoperatively.

In an effort to determine the likely mechanism leading to the disappearance of wave I in case 2, a transtympanic ECochG was carried out. The ECochG recorded from the operated side confirmed the absence of the CAP while both the CM (waveform not shown) and SP were clearly present. Levine et al. (1984) described a very similar situation in a patient with no measurable hearing following VS excision. They

suggested this finding may be associated with retrograde degeneration of the cochlear nerve following its transection during surgery. Several studies have reported that section of the auditory nerve in cats results in a degeneration of ganglion cells but leaves the organ of Corti intact (Schuknecht & Woellner, 1953; Spoendlin & Suter, 1976). Indeed, the time course of ABR changes in the current study is in agreement with observations made during recent animal experiments to investigate this phenomenon. Shimamura et al. (2002) showed that in rats, cochlear nerve degeneration is complete by the end of the first week following nerve compression damage. Studies in humans, however, suggest that cochlear nerve degeneration may have a more variable time course than in animals (Felix & Hoffmann, 1985).

The fact that in case 2 some degree of hearing was maintained in the low frequencies indicates that complete degeneration occurred only in the high-frequency neural fibres. As mentioned above, the high frequency neural impairment observed in case 2 is logical given the superficial position of the high frequency fibres within the nerve (Sando, 1965). In this case, it is possible that these fibres suffered mechanical injury with associated loss of continuity of the axon and encapsulating connective tissue. Alternatively, microcirculation of the capillaries supplying the cochlear nerve may have been disturbed intraoperatively. Why this would selectively affect only high frequency fibres is difficult to explain. Furthermore, histological examination following cochlear nerve compression damage in dogs showed that delayed disappearance of wave I was not due to vascular compromise (Hatayama, Sekiya, Suzuki, & Iwabuchi, 1999). Regardless of initial insult, the massive release of glutamate associated with these

events would have caused excessive influx of calcium into the injured neurons and subsequent cell death (Choi, 1992; Sekiya, Shimamura, Yagihashi, & Suzuki, 2002). As described by Seddon (1943); the injury to the low frequency neural fibres may have been mild enough that the continuity of axons in the endoneurial sheath was preserved and therefore these fibres did not degenerate. Indeed, the slight improvement in low frequency hearing in the days following surgery suggests some recovery of neural function may have occurred. Obstruction of the internal auditory artery in case 2 is extremely unlikely as the presence of the CM and SP provide evidence of retention of function by the stria vascularis and thus, the existence of blood supply to the cochlea.

4.5.2. Prevention of post-operative neuronal degeneration

Given the possibility that cochlear nerve degeneration is responsible for delayed hearing loss, protection from this phenomenon is a potential target for therapeutic intervention. Because axon regeneration cannot occur after neuronal death, the preservation of neural function following trauma to the central process of the cochlear nerve is vital. Preventing intracellular calcium overload by using calcium channel antagonists has been used as a countermeasure to cell death due to nerve trauma (Zornow & Prough, 1996). The calcium channel antagonist nimodipine has shown neuroprotective ability through improvement of cerebral blood circulation and inhibition of calcium overload induced by excessive glutamate release. In addition, nimodipine has also been shown to accelerate axonal sprouting (Angelov et al., 1996). A study conducted by Sekiya, Yagihashi, Asano, & Suzuki (2002) demonstrated that

nimodipine can rescue traumatized cochlear neurons of the rat from degeneration following compressions of the CPA portion of the nerve.

In an attempt to minimize functional deterioration following VS removal in humans, Strauss et al. (2001) carried out a study to investigate whether administration of nimodipine (and hydroxyethyl starch) following surgery improved rates of hearing preservation. Based on their intraoperative ABR pattern, only those patients considered at risk for developing delayed hearing loss due to transient nerve ischemia were included in the study. A comparison of hearing outcomes in the treated and non-treated groups was statistically significant with hearing preserved in 66.6% of the treated group versus 30% on the non-treated group. More recent studies have also reported a statistically significantly better outcome for patients who received prophylactic treatment with nimodipine (and hydroxyethyl starch) following VS surgery (Bischoff, Romstock, Fahlbusch, Buchfelder, & Strauss, 2007; Scheller, Richter, Engelhardt, Koenig, & Antoniadis, 2007). There is some evidence to suggest that this benefit is only experienced by those patients thought to have suffered transient nerve ischemia during surgery (Bischoff, Romstock, Fahlbusch, Buchfelder, & Strauss, 2007). It was proposed that patients with an intraoperative ABR pattern indicative of mechanical trauma of nerve fibres may not respond to treatment due to the more serious nature of their injury. However, delayed hearing loss caused by cochlear damage (due to vascular impairment) cannot be ruled out in these cases.

4.5.3. Enhanced negative SP component

In case 2 of the current study, presence of the CM and SP revealed that the partially deafferentated cochlea was still functioning at 16 weeks following surgery. However, the response recorded from the operated side to both click and tone burst had unusual morphology compared to the non-operated side. In particular, the click evoked potential recorded from the operated ear was abnormally broadened with little evidence of the CAP. When compared to the non-operated side, the tone burst evoked responses confirmed the presence of an enlarged negative SP on the operated side. The persistence of cochlear potentials following VS surgery despite significant cochlear nerve damage has rarely been documented. Levine et al. (1984) reported a case in which neither CAP or ABR were present, but large CM potentials could still be recorded 75 days after removal of a VS. Sabin et al. (1987) recorded the CM and SP from a patient with a deafferentated cochlea 15 months following excision of a VS. More recently, Ohashi et al. (2001) demonstrated the persistence of the SP in a patient 3 years after transection of the vestibulo-cochlear nerve to remove a VS. As in the current study, the response recorded from the operated side to high intensity stimuli (80 dB HL) had unusual morphology and was considered to be mainly composed of an abnormally increased negative SP. This assumption was based on the persistence of the potential despite significantly increasing the repetition rate of the stimulus (clicks and tone bursts) from 10/sec to 50/sec (Ohashi et al., 1996).

Because ECochG was only carried out postoperatively in case 2, it is difficult to determine if the pathological changes within the cochlea were initiated during tumour

growth or VS excision. According to Ohashi et al. (1996; 2001) who carried out ECochG both before and after VS surgery, the broad negative potential was only evident following surgery. Similarly, Zheng, Ding, McFadden, & Henderson (1997) demonstrated an increase of the SP amplitude to high-level stimuli following chemical deafferentation of the cochlea in chinchillas. There are several possible mechanisms that may explain this observation.

The presence of an enhanced SP component is typically considered to be a diagnostic indicator of endolymphatic hydrops (van Deelen, Ruding, Smoorenburg, Veldman, & Huizing, 1988). According to the diagnostic criteria established by Gibson (1993), the absolute amplitude of the SP elicited by 4 kHz tone burst in case 2 indicates the presence of endolymphatic hydrops on the operated side. It is important to note, however, that the sensitivity of this measure appears limited as there is some overlap between patients with "normal" ears and patients with classic symptoms of hydrops. At least one case of confirmed hydrops has been reported in a patient 18 months following VS excision (Kobayashi, Arenberg, Ferraro, & VanderArk, 1993). Indeed, delayed hydrops in the cochlea following tumour removal has previously been investigated as a possible cause of deterioration in preserved hearing (Atlas, Harvey, & Fagan, 1992). In the case of endolymphatic hydrops, an enhanced SP has been correlated with basilar membrane displacement towards scala tympani due to pressure build-up in scala media (Durrant & Dallos, 1974). The resulting change in the operating point of the outer hair cells is thought to add a DC shift to the OHC receptor current, causing an "outer hair cell SP" which sums with the IHC SP. As with Ménière's disease, the underlying cause

of hydrops in case 2 and similar cases is difficult to isolate. Prasher et al. (1995) suggested it may be due to impaired venous drainage. Alternatively, the endolymphatic sac and/or duct may have been violated during surgery (P. Bird, personal communication, January 22, 2008).

It may also be possible that the negative SP enhancement observed in case 2 was induced by inhibition of the efferent nerve system. Takeda et al. (1992) reported that a blockade of the olivocochlear bundle by a local anesthetic causes an enhanced negative SP without apparent changes in the CAP amplitude. In case 2 of the current study, it is possible that injury of the efferent nerve fibres during surgery resulted in an enhanced negative SP. Indeed, given that the cochlear efferent axons travel within the vestibular nerve, they may have been particularly vulnerable to injury during tumour excision. Further study is needed to elucidate the mechanism responsible for the unusual ECochG findings in some patients following VS excision.

5. SUMMARY OF MAIN FINDINGS

The objective of this thesis was to document the patterns of change in behavioural and electrophysiological responses in patients following VS surgery to better describe the phenomenon of delayed hearing loss. In particular, we aimed to determine whether the site of impairment that eventually leads to delayed hearing loss is neural or cochlear in origin. Ultimately it was hoped that from this information, the putative mechanism could be identified and therefore avoided in future. However, from a series of a 6 consecutive patients who underwent surgery for unilateral VS at Christchurch hospital via the retrosigmoid approach, there were no cases of delayed hearing loss observed. Instead, this study found that 4 patients suffered permanent anacusis and the remaining 2 patients had permanent hearing preservation. Based on the limited data available in the literature, the chance of observing delayed hearing loss in a group of 6 patients is unlikely.

Although delayed hearing loss was not documented in the current study, a similar phenomenon was observed in case 2 who demonstrated loss of ABR wave I on the 7th postoperative day. As with delayed hearing loss, the deterioration of wave I long after surgical manipulation had ended suggests a pathophysiological mechanism initiated during surgery that continued postoperatively. As cochlear function was still evident at 16 weeks following surgery, it was proposed that the loss of wave I was caused by retrograde degeneration of the high frequency cochlear nerve fibers. Retrograde degeneration in this case was almost certainly a result of direct mechanical trauma to

the central portion of the nerve during surgery. The selective loss of only high frequency neural fibers was most likely related to their superficial position within the nerve (Sando, 1965), making them more prone to injury during surgical manipulation. Surprisingly, the postoperative ECochG findings recorded in case 2 showed an enhanced negative SP on the operated side. This finding may reflect the loss of tonic efferent activity due to severance of efferent neural connections during surgery. Alternatively, the presence of an enhanced SP component could be a diagnostic indicator of endolymphatic hydrops.

In both cases where hearing was preserved, a substantial drop in auditory function occurred following VS excision. Although the etiology of hearing impairment in these cases was neural in origin, the specific nerve fibres affected during tumour removal appeared to be dependent on the location of the tumour. A gradual improvement in neural-auditory function following surgery was demonstrated in both cases. This finding provides evidence that the cochlear nerve has a certain capacity to recover during the postoperative period following VS excision.

The cochlear nerve was not considered to be anatomically preserved in any case suffering postoperative anacusis. Patients suffering anacusis who had preoperative cochlear function lost this following surgery. Loss of cochlear function was most likely the result of a transient interruption in blood supply due to vasospasm or embolism of the IAA during surgery. Although the number of patients in this study was limited, cases suffering anacusis postoperatively tended to have larger sized tumours, worse

hearing and poorer word recognition prior to surgery. In terms of preoperative auditory function, all patients in the current study demonstrated some degree of high frequency cochlear impairment in addition to neural dysfunction.

5.1. Clinical implications

Given that the findings of this study were based a single subject design, they are not viable at a clinical level, however, future clinical implications can be predicted. The risk for delayed anatomical and functional impairment of the cochlear nerve after VS excision has been demonstrated in case 2 of the current study. Similar electrophysiological findings in this case and cases of delayed hearing loss (Strauss et al., 1991) suggest a common mechanism. Based on this assumption, cochlear nerve degeneration is a potential target for therapeutic intervention. Thus, administration of a neuroprotective agent such as nimodipine might possibly be of benefit to patients following VS surgery. However, such treatment may only be of benefit to patients who have suffered transient nerve ischemia; patients with more severe nerve injury may not be responsive (Bischoff, Romstock, Fahlbusch, Buchfelder, & Strauss, 2007). In terms of avoiding severe nerve injury, changes in surgical technique or the use of intraoperative auditory system monitoring may prove most effective.

5.2. Limitations

The fact that delayed hearing loss was not observed in any patient following VS surgery has been attributed to the small number of participants, a major limitation of this preliminary study. However, given the low incidence of VS together with the time

constraints of this thesis, such a small patient group was considered unavoidable. As the current study is part of an ongoing research, the inclusion of more participants over time will eventually overcome this obvious limitation.

Transtympanic ECochG was used in the present study to determine whether postoperative deterioration in auditory function was neural or cochlear in origin. Due to the limited availability of a physician with the time and experience to perform electrode placement, ECochG was only carried out at the 16 week postoperative assessment. For this reason, it is difficult to establish whether pathological changes within the cochlea were initiated during tumour growth or VS excision. Furthermore, this method did not provide any indication of the time-course of these pathological changes.

As highlighted in case 2 of the current study, the potential exists for patients to suffer delayed auditory impairment up to 7 days following VS excision. Several patients monitored during this study were discharged from hospital on postoperative day 6. It is therefore conceivable that delayed hearing loss may take place after hospital discharge. Although detection of the hearing loss at the 16 week follow-up assessment is expected, there would be no indication of when it occurred and over what time-course the changes took place. This potential limitation should be addressed in future studies so that cases of delayed hearing loss are not missed.

To better understand the relatively rare phenomenon of postoperative delayed hearing loss and its associated mechanism, a single case study design was considered appropriate. However, the intention of using this type of experimental approach naturally presents certain limitations regarding the generalisation of the results. Before conclusive results are generalized, it will be necessary to carry out further study so that in-depth observation and analysis of multiple cases of delayed hearing loss can be made.

5.3. Directions for future research

As postoperative delayed hearing loss was not observed during the current study, we are still not able to fully define this phenomenon or determine a likely mechanism. Although recent studies conducted by Strauss and colleagues (2007; 2001) seem to suggest a neural site of impairment, delayed hearing loss resulting from damage to the cochlea due to vascular impairment cannot be ruled out. For this reason, ongoing research is required to document the patterns of change in behavioural and electrophysiological responses in patients suffering delayed hearing loss following VS surgery. Although not possible in the current study, intraoperative monitoring of auditory potentials may prove useful in terms of identifying at what stage during surgery hearing is initially affected. Once the mechanism of hearing loss is more clearly elucidated, future research can address the benefit of targeted therapeutic approaches and improved surgical technique.

Although the primary objective of this thesis was not achieved, our findings have highlighted other possible avenues for future research. In case 2 of the current study, ECochG following VS excision revealed an enhanced SP component. Although a number of similar cases have been reported in the literature (Ohashi et al., 2001; Sabin, Prasher, Bentivoglio, & Symon, 1987), the underlying mechanism remains unknown. Injury of the efferent nerve fibers and the resulting inability to modulate cochlear and cochlear nerve excitability may increase vulnerability to acute acoustic injury in these patients. Therefore, future studies should consider investigating the mechanism underlying the enhanced SP component recorded in some VS cases following surgery.

Findings from the current study also demonstrated that mean tumour size was considerably larger in our group of patients than has recently been reported by several large-scale studies (Chen, 2007; Stangerup et al., 2004; Tos, Stangerup, Caye-Thomasen, Tos, & Thomsen, 2004). Early detection of VS is important as patients with small tumours have a lower risk of morbidity and higher chance of preserving their hearing following surgery. Further research is needed with more participants to investigate whether tumour size in the population of patients presenting for VS surgery at Christchurch Hospital is indeed larger than “normal” and the underlying reason/s for this.

Finally, future studies concerning hearing preservation following VS excision should consider the fact that changes in auditory function can occur during the early

postoperative period. This is particularly relevant when rates of hearing preservation are reported.

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APPENDIX I

Health Research Council ethics approval letter

Human Ethics Committee approval letter

Research information form

Consent form

22 May 2007

Mr P. A. Bird
Dept of Otolaryngology
Christchurch Public Hospital
Private Bag 4710
Christchurch

Dear Mr Bird,

Patterns of hearing loss during and following the removal of acoustic neuroma
Investigators: Mr P Bird, Dr A Scarlett, Dr G O'Beirne, Mr M MacFarlane, Ms M Feldman
Locality: Christchurch Hospital
Ethics ref: URA/07/03/017

The above study has been given ethical approval by the **Upper South A** Ethics Committee. A list of members of this committee is attached.

Approved Documents
Information sheet and consent form version 2 dated 16 April 2007

Certification
The Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out.

Accreditation
The Committee involved in the approval of this study is accredited by the Health Research Council and is constituted and operates in accordance with the Operational Standard for Ethics Committees, April 2006.

Progress Reports
The study is approved until 1 June 2009. The Committee will review the approved application annually and notify the Principal Investigator if it withdraws approval. It is the Principal Investigator's responsibility to forward a progress report covering all sites prior to ethical review of the project in June 2008. The report form is available on http://www.newhealth.govt.nz/ethicscommittees. Please note that failure to provide a progress report may result in the withdrawal of ethical approval. A final report is also required at the conclusion of the study.

Requirements for SAE Reporting
The Principal Investigator will inform the Committee as soon as possible of the following:

- Any related study in another country that has stopped due to serious or unexpected adverse events
- withdrawal from the market for any reason
- all serious adverse events occurring during the study in New Zealand which result in the investigator or sponsor breaking the blinding code at the time of the SAE or which result in hospitalisation or death.
- all serious adverse events occurring during the study worldwide which are considered related to the study medicine. Where there is a data safety monitoring board in place, serious adverse events occurring outside New Zealand may be reported quarterly.

All SAE reports must be signed by the Principal Investigator and include a comment on whether he/she considers there are any ethical issues relating to this study continuing due to this adverse event. If the adverse event is local and does not have the sponsor's report attached, an opinion on whether the event is thought to be related to the study should be given along with any other pertinent information. It is assumed by signing the report, the Principal Investigator has undertaken to ensure that all New Zealand investigators are made aware of the event.

Amendments

All amendments to the study must be advised to the Committee prior to their implementation, except in the case where immediate implementation is required for reasons of safety. In such cases the Committee must be notified as soon as possible of the change.

Please quote the above ethics committee reference number in all correspondence.

It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. Where applicable, authority for this must be obtained separately from the appropriate manager within the organisation.

We wish you well with your study.

Yours sincerely

Alieke Dierckx
Upper South A Ethics Committee Administrator

Email: alieke_dierckx@moh.govt.nz
List of members of the Upper Region A Ethics Committee, March 2007

Carolyn Mason (Chair)	Ethicist/Philosopher Lay member	Female
Carolynn Bull	Legal representative, Maori representative Lay member	Female
John Horwood	Biostatistician Lay member	Male
Jane Kerr	Researcher Health Professional Member	Female
Alison Luckey	Health Practitioner Health Professional member	Female
Tom Marshall	Clinical Psychologist Health Professional member	Male
Ellen McCrae	Pharmacist Health Professional member	Female
Edie Moke	Maori representative Lay member	Female
Nicky Murray	Community Representative Lay member	Female
Elizabeth Richards	Consumer Representative Lay member	Female
Russell Scott	Health Practitioner Health Professional member	Male

Carolynn Bull and Edie Moke were not present at the meeting on 26 February 2007.

Alieke Dierckx (Administrator) Date

HEC Ref: 2007/45

22 May 2007

Melanie Feldman
Communication Disorders
UNIVERSITY OF CANTERBURY

Dear Melanie

The Human Ethics Committee advises that your research proposal "Early postoperative hearing loss following vestibular schwannoma surgery: behavioural and electrophysiological responses" has been considered and approved. However this approval is subject to the amendments you outlined in your email of 18 May 2007.

Yours sincerely

Dr Michael Grimshaw
Chair, Human Ethics Committee

INFORMATION FORM

PATTERNS OF HEARING LOSS DURING AND FOLLOWING THE REMOVAL OF ACOUSTIC NEUROMA
February 2007

Introduction
You are invited to take part in this study during your surgery for removal of an acoustic neuroma. Your decision to take part can be made at any time between reading this form and the day of your operation. You do not have to take part in this study. If you do agree to take part you are free to withdraw from the study at any time, without having to give a reason and this will in no way affect your future/continuing health care. All people undergoing surgery to remove an acoustic neuroma with possible hearing preservation over the next two years will be asked to participate in this study. This will involve approximately 25 to 40 people.

Why is this study being done?
With the use of magnetic resonance imaging (MRI), people are presenting earlier with acoustic neuromas than previously. Subsequently many people still have a reasonable level of hearing prior to the removal of the acoustic neuroma. Unfortunately one of the risks of surgery includes reduction/loss in functional hearing. This study will monitor the patients hearing before, during and following surgery in order to determine the stage at which hearing is lost (if at all). The results from this study will be used to help surgeons understand why people can lose their hearing following acoustic neuroma surgery. If it can be established at which point during the operation hearing is lost (if at all), then more research can be aimed at changes in the techniques/approaches that surgeons use, in order to reduce the risks of hearing loss.

What do we plan to do during the study?
A variety of methods will be used to assess your hearing prior to surgery, all of which will cause no discomfort to you. Most of the assessments are routine prior to surgery regardless of your involvement in the study. During the operation when you are under a general anaesthetic your brain will still respond to sounds the same as when you are awake. We can pick up this activity from your brain using “electrodes” (wires connected from a computer to an adhesive patch which is placed on your skin). This technique of monitoring hearing is not usually performed in routine removal of an acoustic neuroma. Following the surgery hearing assessments will be made every hour for the first six hours then twice daily until you are discharged from hospital. Involvement in this study will not delay your recovery or discharge from hospital. Following surgery you would usually undergo such tests on one occasion, however for the purposes of this study, such tests will be repeated more frequently. Although your hearing will be monitored immediately following surgery, this will only require you to be involved physically in the assessments (eg listening for sounds etc), if you are awake and happy to participate. If your hearing is lost during the postoperative period, a specialized test will be carried out following the operation. This would involve a drop

of medicine to numb a part of your ear drum and then a tiny needle would be inserted into the eardrum. This would detect whether the inner ear is picking up any sound even if you are unable to subjectively hear anything. This test is not usually routine. Although no extra visits to the department will be required, the tests will take extra time during routine follow ups. The hearing tests will be carried out by Ms Feldman, an audiology Masters student.

Is there any risk to me to be involved in this study?
We do not anticipate any increased risk from being involved in this study over and above the risks involved with removal of an acoustic neuroma. The only hearing assessment which can be slightly uncomfortable is the specialized test which requires a drop of anaesthetic onto the ear drum which will be done if hearing is lost in the period following the operation.

Will this study help me?
This study will not directly help you but may help people in the future undergoing a similar operation, to preserve their hearing. If we can detect when hearing loss occurs, methods may be developed to prevent it from occurring.

Everyone who participates in this study will receive feedback as to how the study has gone in the future.

No material which could personally identify you will be used in any reports on this study.

It is a requirement that all health research data must be stored for 10 years in the case of adults.

This study has received ethical approval from the Upper South A Regional Ethics Committee and the University of Canterbury Human Ethics Committee.

If you have any queries or concerns regarding you rights as a participant under this study you may wish to contact a Health and Disability Advocate, telephone

- South Island except Christchurch 0800 377 766
- Christchurch 03 377 7501

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ASS according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. Acc usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. If you have ACC cover, generally this will affect your right to sue the investigations. If you have any questions about AC, contact your nearest ACC office or the investigator.

If you have further questions or would like to discuss the research further, please do not hesitate to contact the researchers

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Dr Greg O'Beirne
Lecturer in Audiology
03 364 2987 ext. 7085

Ms Melanie Feldman
Audiology Masters Student
03 364 2987 ext. 7085

CONSENT FORM

PATTERNS OF HEARING LOSS DURING AND FOLLOWING THE REMOVAL OF ACOUSTIC NEUROMA
May 2007

REQUEST FOR INTERPRETER

English	I wish to have an interpreter	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Samoan	Ou te manaó ia I ai se faámatala upu.	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Ioe	Ikai
Cook Island	Ka inangaro au I tetai tangata uri reo.	Ae	Kare
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai
Mandarin	我需要一个翻译	对	不对
Japanese	通訳の人を希望します。	はい。	いいえ。
Korean	통역이 필요 하세요?	네	아니오

1 I have read and I understand the information sheet (dated 16th April 2007) for volunteers taking part in the study designed to investigate patterns of hearing loss during and following the removal of an acoustic neuroma. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

2 I have had the opportunity to use whanau support or a friend to help me ask questions and understand the study.

3 I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without having to give a reason and this will in no way affect my continuing health care

4 I have had this project explained to me by the principal investigator Mr Phil Bird.

5 I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports in this study.

6 I understand that the investigation will be stopped if it should appear harmful to me.

7 I have had time to consider whether to take part

8 I know who to contact if I have any side effects to the study.

9 I know who to contact if I have any questions about the medication or the study.

10 I wish to receive a copy of the results yes/no

11 I would like the researcher to discuss the outcomes of the study with me yes/no

12 I agree to my GP or other current provider being informed of my participation in this study yes/no

I ……(full name) hereby consent to take part in this study

to investigate patterns of hearing loss during and following the removal of an acoustic neuroma

Signature ……..Date …….Time ……

Study explained an consent witnessed by ……..(full name)

Signature ……..Date …….Time ……

APPENDIX II

Audiological findings for cases of postoperative anacusis:

-Case 3

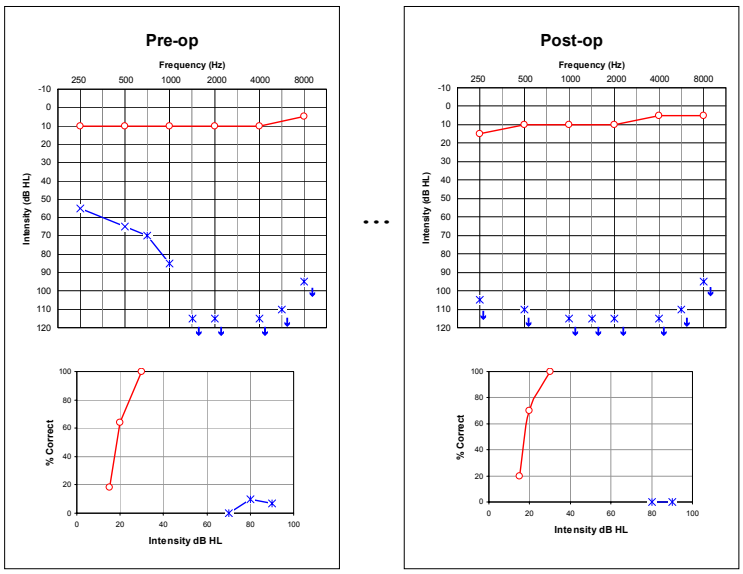
-Case 4

-Case 5

-Case 6

CASE 3: Preoperative and postoperative audiologic evaluation including pure-tone audiometry (A), DPOAEs (B) and ABR (C).

A.

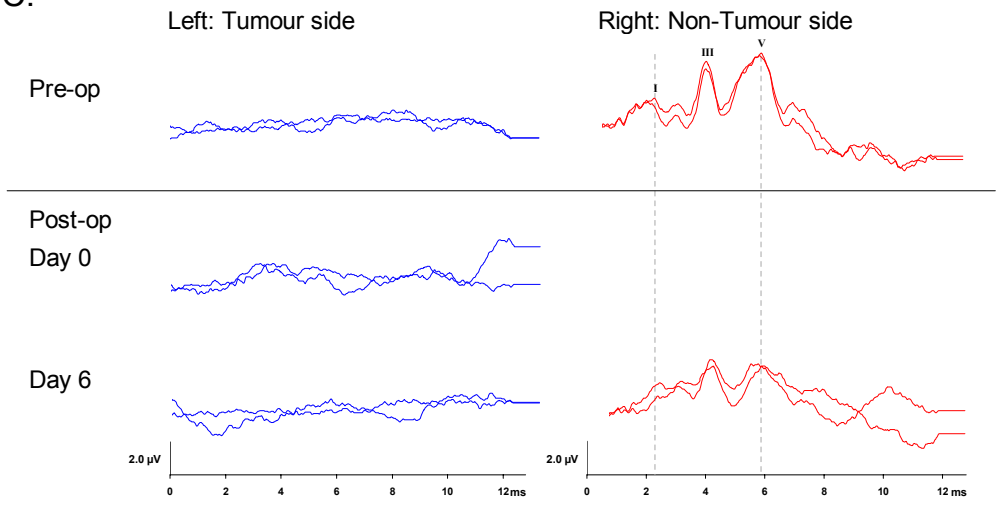


B.

Pre-op DPOAEs		f_2 (Hz)					
		1000	1500	2000	3000	4000	6000
SNR	*Right*	+	+	+	+	+	+
	Left	-	-	-	-	-	-

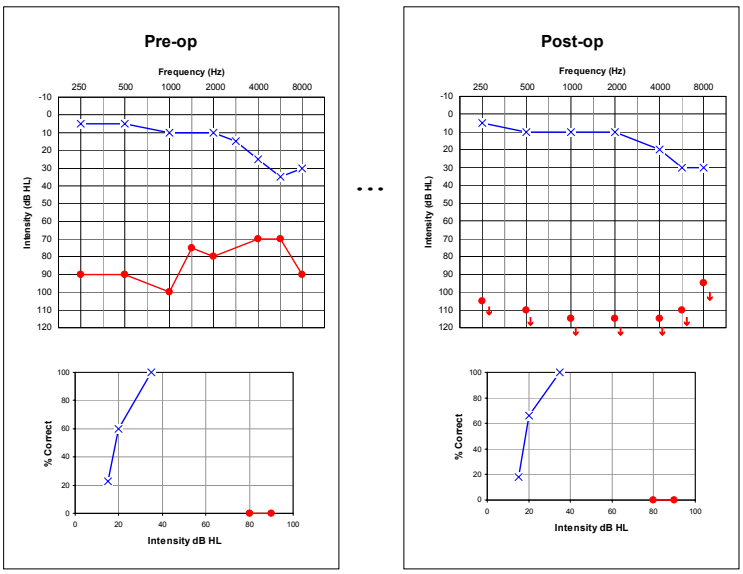
Post-op DPOAEs		f_2 (Hz)					
		1000	1500	2000	3000	4000	6000
SNR	*Right*	+	+	+	+	+	+
	Left	-	-	-	-	-	-

C.



CASE 4: Preoperative and postoperative audiologic evaluation including pure-tone audiometry (A), DPOAEs (B) and ABR (C).

A.

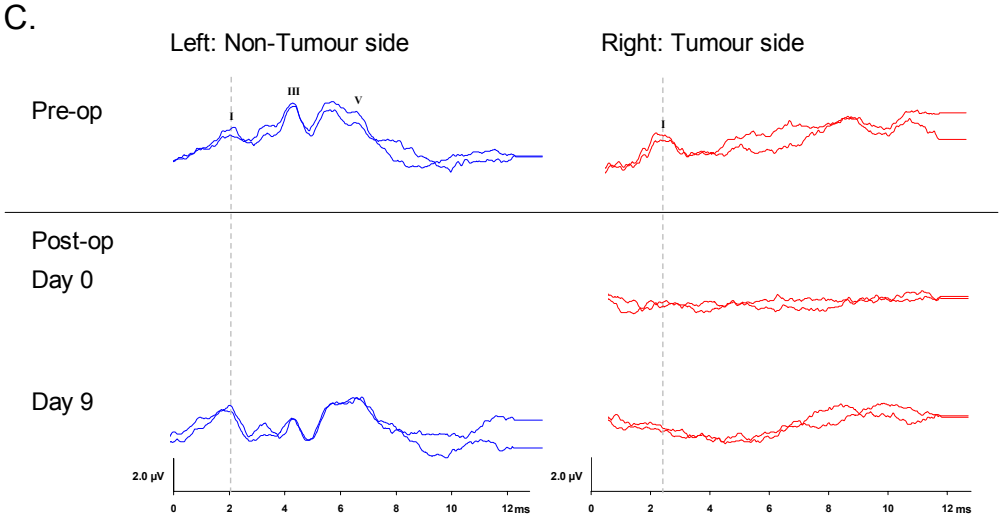


B.

Pre-op DPOAEs		f_2 (Hz)					
		1000	1500	2000	3000	4000	6000
SNR	*Right*	+	+	+	+	-	-
	Left	+	+	+	+	+	-

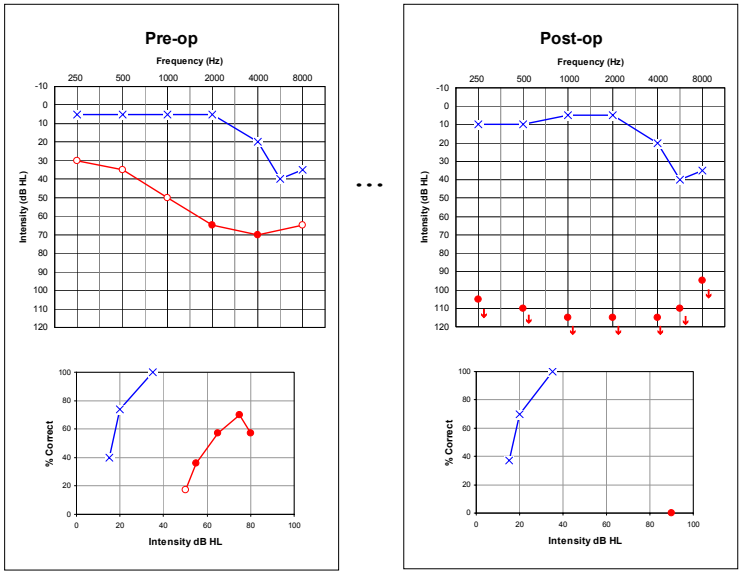
Post-op DPOAEs		f_2 (Hz)					
		1000	1500	2000	3000	4000	6000
SNR	*Right*	-	-	-	-	-	-
	Left	+	+	+	+	+	-

C.



CASE 5: Preoperative and postoperative audiologic evaluation including pure-tone audiometry (A), DPOAEs (B) and ABR (C).

A.

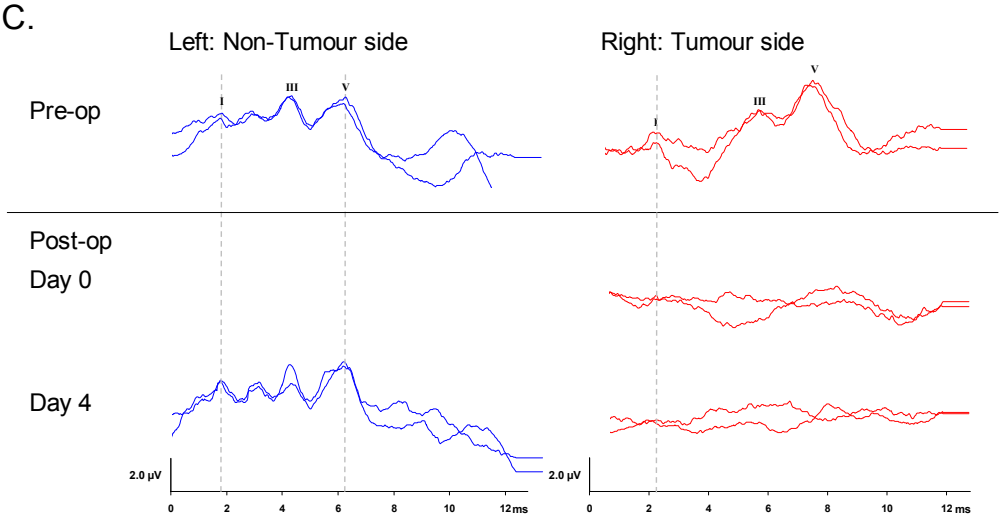


B.

Pre-op DPOAEs		f_2 (Hz)					
		1000	1500	2000	3000	4000	6000
SNR	*Right*	+	+	-	-	-	-
	Left	+	+	+	+	+	-

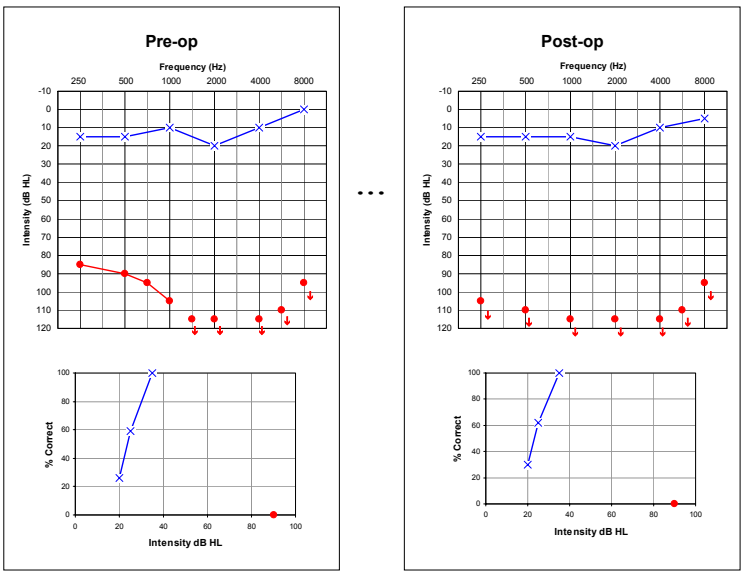
Post-op DPOAEs		f_2 (Hz)					
		1000	1500	2000	3000	4000	6000
SNR	*Right*	-	-	-	-	-	-
	Left	+	+	+	+	+	-

C.



CASE 6: Preoperative and postoperative audiologic evaluation including pure-tone audiometry (A), DPOAEs (B) and ABR (C).

A.



B.

Pre-op DPOAEs		f_2 (Hz)					
		1000	1500	2000	3000	4000	6000
SNR	*Right*	-	-	-	-	-	-
	Left	+	+	+	+	+	+

Post-op DPOAEs		f_2 (Hz)					
		1000	1500	2000	3000	4000	6000
SNR	*Right*	-	-	-	-	-	-
	Left	+	+	+	+	+	+

C.