ACTION POTENTIAL LATENCY IN INDIVIDUALS WITH ENDOLYMPHATIC HYDROPS

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A Dissertation Submitted in Part Fulfillment of Final Year

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CERTIFICATE

This is to certify that this dissertation entitled ***"Action potential latency in individuals with endolymphatic hydrops"*** is a bonafide work submitted in part fulfilment for the degree of Master of Science (Audiology) of the student Registration No.: 10AUD011. This has been carried out the under guidance of a faculty of this institute and has not been submitted earlier to any other university for the award of any diploma or degree

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This is to certify that this dissertation entitled ***"Action potential latency in individuals with endolymphatic hydrops"*** has been prepared under my supervision and guidance. It is also certified that this dissertation has not been submitted earlier to any other university for the award of any diploma or degree.

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DECLARATION

This is to certify that this master's dissertation entitled ***"Action potential latency in individuals with endolymphatic hydrops"*** is the result of my own study under the guidance of **Mr. Niraj Kumar Singh**, Lecturer in Audiology, Department of Audiology, All India Institute of Speech and Hearing, Mysore, and has not been submitted earlier to any other university for the award of any diploma or degree.

Mysore

May, 2012 **Register No. 10AUD011**

DEDICATED TO..

Attukal devi, for being my strength…

Achan, amma, annan for the love….

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INTRODUCTION

Electrocochleography (ECochG)is a technique of recording stimulus related responses or the electrical potentials of the inner ear and auditory nerve. It is employed to evaluate cochlear function in patients with Meniere's disease. The underlying pathologic finding in Meniere's disease is widely suspected to be endolymphatic hydrops, which has been shown in animal studies to systematically alter cochlear potentials (Kimura, 1982; Aran, Rarey, &Hawkins, 1984).

The cochlear potentials of interest in clinical ECochG are the eighth nerve compound action potential (AP), the summating potential (SP) and the cochlear microphonics (CM). The AP results from simultaneous, stimulus-locked discharge of a population of spiral ganglion neurons (Kiang, 1965; Cullen, Ellis, & Berlin, 1972).The SP is a stimulus-locked direct current potential that can be observed as a baseline shift in the CM, and is also generated by cochlear hair cells(Dallos, 1973). The CM is an electrical response that mimics the acoustic waveform of the stimulus and is generated by the cochlear hair cells (Dallos, 1973).

A variety of electrode locations have been employed to record these potentials in animal and human investigations. In animal studies, electrodes are commonly placed in the cochlea (Van Deelen&Smoorenburg, 1986), on the round window (Prijs, 1985) or directly on the auditory nerve (Kiang, 1965). In humans, three electrode sites have been employed. Transtympanic ECochG is performed by placing a needle electrode through the tympanic membrane and onto the promontory (Moffat, Gibson, Ramsden, Morrison, & Booth, 1977).

Tympanic ECochG employs an electrode that is placed on the tympanic membrane (Margolis, Rieks, Fournier, & Levine, 1995). Extratympanic ECochG is performed with an electrode placement in contact with the ear canal wall (Mori,Asai, &Matsunaga, 1987). These electrode sites tend to impact the morphology of the thus recorded ECochG waveform. In general, response amplitudes diminish with increasing distance from the cochlea (Eggermont, Odenthal, Schmidt, & Spoor, 1974).

The ECochG has been used for the diagnosis of several auditory pathologies. These include auditory dys-synchrony (Roland, Yellin, Meyerhoff, & Frank, 1995;Santarelli&Arslan, 2002;Anastasio, Alvarenga,&Filho,2008)and also Meniere's disease (Aso, Watanabe, &Mizukoshi, 1991; Mori, Asai, Suizu, Ohta, &Matsunaga, 1985; Mori, Asai, &Matsunaga, 1987; Ferraro &Tibbils, 1999;Saas, Densert, Magnusson, &Whitaker 1998) among others.

Need for the study

Literature is brimming with reports regarding the use of various tests that have been deployed for the diagnosis of Endolymphatic hydrops (EH). These include Glycerol test, Vestibular Evoked Myogenic Potential (VEMP),Cochlear Hydrops Analysis Masking Procedure (CHAMP), and Electrocochleography (ECochG). In addition auditory brainstem responses have only shown their usefulness in ruling out retrocochlear lesions and do not exactly are advocated for the diagnosis of Meniere's disease. Glycerol test has been used in conjunction with many tests like Pure tone audiometry (Karjalainen, Karja, & Nuutinen,1977), Speech audiometry (Karjalainenet al.,1977),OAE (Maqliulo, Cian, Triches, &Altissimi, 2001), ECochG (Moffat, Gibson, Ramsden, Morrison, & Booth, 1977; Kitaoku, 1994), and VEMP (Ban, Lee, Jin, &Lee, 2007) and has been found to be useful in the diagnosis of Meniere's disease.

The sensitivity of glycerol test in conjunction with pure tone audiometry has been reported to range between 54.5% and 83.3 % (Kotimaki, Sorri, &Muhli, 2003; Zhao, Zhu, &Lui. (2005). Theoutcome of the glycerol test in patients with Meniere's disease depends on the pre-test threshold levels. If the hearing loss is mild or moderate, the number of negative test results increase (Karjalainen et al., 1977). Also, if the degree of hearing loss is severe or more, then the negative results tend to increase (Snyder, 1974). Moreover, the test is associated with an unpleasant side effect, including headache, nausea, thirst, diarrhoea and dizziness (Futaki, Kitahara, &Morimoto, 1977). In addition, the testing should be administered in the presence of Otolaryngologist or any other medical practitioner, which is not always possible in most audiological clinics and is also contraindicated in patients with diabetes (Snyder, 1974).

VEMP has been found to be a useful tool for the diagnosis of Meniere's disease. In patients with Meniere's disease VEMP may have reduced amplitude, they may be absent or, paradoxically, the amplitude of the VEMP may be abnormally large occasionally (Young, Huang, & Cheng, 2003). However, these findings are not specific only to Meniere's disease, rather they are also observed in other unilateral vestibular pathologies like vestibular neuritis and labyrinthitis(Welgampola& Colebatch, 2005). Abnormal asymmetry in VEMP amplitude is the distinctive clinical finding associated with most unilateral vestibular dysfunctions that affect the sacule or inferior vestibular nerve (Halmagyi, Colebatch &Curthoys, 1994). So, findings of VEMP alone might just be an indicator of unilateral pathology but in no way it can be specific to Meniere's disease.

Another test is Cochlear Hydrops Analysis Masking Procedure (CHAMP) which is utilised for the diagnosis of Meniere's disease. However, the sensitivity and specificity of CHAMP has been reported to be a subject of controversies in the literature. Lee, Park, Hong, and Kim (2011) reported the sensitivity values of 85.7% and specificity of87.5%. Contrary to their findings,

Ordonez, Rojas, and Hernandez (2009) reported a poorer sensitivity value of 32%. The inconsistencies across the findings make CHAMP a not so useful technique for the diagnosis of Meniere's disease atleast in its current status.

Yet another test that has been reported to be useful in the diagnosis of Meniere's disease is ECochG. The important parameters used are area ratio of Summating Potential to Action Potential and also their amplitude ratio (SP/AP). In Meniere's disease SP/AP is reported to be enlarged (Gibson &Conlon, 1994). However, the SP is reported to be present only in 60-65% of normal (Zeng, Ding, McFadden, &Henderson, 1998; Sinha&Vanaja, 2005-06) which would restrict the use of these ratios for diagnosis of MD.

As can be seen from the above mentioned tests and their findings, the diagnosis of Meniere's disease (EH) is a difficult proposition. This,though, may be aided by the action potential of ECochG. The action potential of ECochG is reported to be present in all individuals with hearing loss not exceeding 50-60 dB (Chiappa, Gladstone, & Young, 1979). The shift in latency from rarefaction to condensation polarity is reported to be 0.2msor less in normals (Saas,Densert, Magnusson, & Whitaker, 1998;Chen, Kang, Yeh, &Wang,2004). Since there is altered mechanism of movement of the basilar membrane due to increased pressure from the excessive amount of endolymph present in the cochlear duct, there is likelihood of change in the latency difference from one to the other polarity as the pressure would impact one polarity (condensation) more than the other (rarefaction) (Tonndorf, 1975). In a preliminary study by Margolis, Rieks, Fournier and Levine (1995), the authors reported increased difference in the latency of action potential between rarefaction and condensation polarities in individuals with Meniere's disease. However, the clinical group in the above study was very restricted which calls for a need for this to be explored further. In addition, the study also used a transtympanic

electrode placement which is nearly impossible in an outpatient audiologic set up. These kinds of set-ups conduct ECochG using extratympanic placement of the non inverting electrode. Hence, it needs to be explored if the effectiveness of the AP latency difference technique would continue to be same for this kind of placement.

Also, theAP ofECochG corresponds to the wave I of the Auditorybrainstem response (ABR)(Moller &Janetta, 1983; Hall &Antonelli, 2001) and this is reported to be present in nearly all individuals with hearing loss not exceeding 50-60 dB (Chiappa, Gladstone, & Young, 1979). So a shift of latency from rarefaction to condensation due to changes in basilar membrane properties may be likely to show up as similar changes in ABR wave I latency. However, such kind of use of an ABR technique has not yet been explored.

Aim of the study

The above inadequacy of various tests in the diagnosis of Meniere's disease calls for further studies that could aid its diagnosis. So, the present study was conducted with the following objectives:

- To compare the latency shift of the APpolarities between ears of healthy individuals and their counterparts with Meniere's disease.
- To compare the latency shift of the AP polarities between ears of healthy individualsand ears of individuals with sensorineural hearing loss
- To compare the latency shift of the AP polarities in ears with sensorineural hearing loss and those with Meniere's disease.
- To compare SP/AP amplitude ratio and shift in latency between the polarities, the two measures of ECochG that identify Meniere's disease.

- To compare the latency shift of the wave I latency of ABR between condensation and rarefaction polarities between ears of healthy individuals and those with Meniere's disease.
- To compare the latency shift of the wave I latency of ABR between condensation and rarefaction polarities between ears of healthy individuals and those with sensorineural hearing loss.
- To compare the latency shift of the wave I of ABR between condensation and rarefaction polarities between ears with sensorineural hearing loss and those with Meniere's disease.

Chapter-2

REVIEW OF LITERATURE

Endolymphatic hydrops is a condition resulting from excessive accumulation of endolymph in the cochlear and vestibular labyrinths. This excessive accumulation of endolymph often causes Meniere's disease, which presents with a constellation of symptoms of episodic vertigo, hearing loss, tinnitus and aural fullness. The name of this syndrome is derived from the French scientist, Prosper Meneire, who first attributed the diverse symptoms of dizziness, vomiting, and hearing loss to a disorder of the inner ear rather than the central nervous system in 1861.

Meniere's disease has been defined as "a disease of deafness, vertigo, and usually tinnitus having as its pathologic correlate hydropic distension of the endolymphatic system" (Alford, 1972). In 1985 the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) agreed to be restrictive and to include only those cases with the full complement of classic symptoms and findings of the disease presumed to result from idiopathic Endolymphatic Hydrops.

Meniere's disease usually presents with a history featuring the tetrad of symptoms that include attacks of rotatory vertigo accompanied by nausea or vomiting, fluctuating sensorineural hearing loss triggered by attacks but may become permanent later, tinnitus with broadband noise like quality, and deep aural pressure that generally precedes the attack. The attacks may have variable frequencies ranging from 1- 2 times a day to occasionally once a month and rarely once in a few months(Klockhoff, &Lindblom, 1961; Paparella, 1995).

Monsell, Balkany, Gates,Goldenberg,Meyerhoff, and House (1995), as part of the committee ofthe American Academy of Otolaryngology – Head and Neck Surgery, had classifiedMeniere's disease in to definite, certain, probable and possible based on symptoms and test results. An individual is recommended to be put in to 'definite' category if there has been two or more episodes of vertigo lasting for over 20 minutes, has tinnitus or aural fullness, audiometry shows sensorineural hearing loss atleast on one occasion, and other causes of such precipitations have been ruled out. A 'certain' Meniere's disease would be the one where 'definite' Meniere's disease has been confirmed through histopathological findings. The individuals under 'probable' category would be those with atleast one definite episode of vertigo regardless of duration, tinnitus or aural fullness, and audiometrically documented hearing loss atleast once with other causes of such presentations being ruled out. The fourth category is 'possible' Meniere's disease which is recommended to include those individuals who have rotatory vertigo without documented hearing loss or sensorineural hearing loss of fluctuating or fixed type without episodic nature to their vertigo or dysequillibrium.

The classification of Meniere's disease based on AAO-HNS (1995) is based on only the clinical symptoms and audiometry results. However, several other tests have been reported to project specific findings in Meniere's disease. These include pure tone audiometry, speech audiometry, special tests like SISI, glycerol test, Otoacoustic emissions, Vestibular Evoked Myogenic Potentials, Cochlear Hydrops Analysis Masking Procedure, and Electrocochleography.

Pure tone audiometry

Meniere's disease has been reported to be associated with sensorineural hearing loss of different configurations. The most common pattern is the rising pattern with hearing loss maximal in the low frequencies. This is seen in the early stagesof the disease (Klockhoff, &Lindblom, 1961; Enander,&Stahle, 1967). When the endolymph volume is increased, basilar membrane forms its maximum distention near its apical end where stiffness is least. Increased endolymphatic fluid volume could mechanically alter travelling wave, and cause a loss in sensitivity due basilar membrane displacement at low frequencies (Tonndorf, 1975). However, a low frequency sensorineural hearing loss need not always be an indicator of Meniere's disease. Such raising patterns have also been documented with brainstem tumors (Jerger&Jerger, 1975) and several other pathologies. Further, Meniere's disease has also been reported to present with flat hearing loss (Savastano, Guerrieri, &Marioni, 2006; Kotimaki,Sorri,&Muhli, 2003) and occasionally slightly sloping hearing loss in the later stages of the disease(Savasto et al, 2006; Kotimaki, 2003). Hence, the configuration of hearing loss cannot specifically be used for confirmation of a diagnosis of Meniere's disease.

Speech audiometry

The characteristic finding in severe Meniere's disease is that of worsening of the discrimination scores with increasing speech level of the speech stimuli (Paparella, 1995). The discrimination difficulty is attributed to the distortion produced in the cochlea.However, such findings have also been reported in certain other pathologies like acoustic neuromas and other retrocochlear lesions (Meyer&Mishler, 1985) and thus do not warranty the diagnosis of Meniere's disease.

Otoacoustic emission (OAE)

OAEs are produced from cochlea and Meniere's disease is disease of the inner ear, hence the likelihood of it being detected by OAE should be higher. Several studies have reported the findings of OAE in individuals with Meniere's disease. Some patients with sensorineural hearing loss due to Meniere's disease have transient evoked OAEs (TEOAEs) or distortion product OAEs (DPOAEs) with normal or even greater than expected amplitude values, even with thresholds exceeding 30 dB HL, and in selected cases, up to 60 dB HL (Ohlms, Martin, & Martin, 1973; Harris &Probst, 1992).

Huffelen, Mateijsen, and Wit (1998) obtained four patterns of distortion product OAEs in patients with Meniere's disease and classification of Meniere's disease was done on the basis of that. Click evoked OAEs (CEOAEs) and DPOAEs were obtained in both ears of 70 individuals with Meniere's disease. In patients with hearing loss less than 30dB, OAEs were present and in those with loss greater than 60dB OAEs were absent. For hearing loss between 30 and 60dB two types of patterns were obtained; one group had otoacoustic emissions (occurrence of these OAEs could be due to the presence of small undamaged regions on the basilar membrane) and other group had no measurable emissions. Also, in Meniere's patients with contralateral ear having normal hearing thresholds, OAEs were smaller than normal hearing adults suggesting very early manifestation of bilateral Meniere's disease, which cannot be detected by other diagnostic methods.

Though a finding of presence of OAEs even in presence of higher degrees of hearing loss may be an encouraging sign for the identification of Meniere's disease, it does not always have a one-to-one correspondence. In addition, similar findings may also be present in eighth nerve

tumors (Kim, Yoon, Chung, & Lee, 1998; Telischi, 2000) and auditory neuropathy spectrum disorders (Starr, Picton,Sininger, Hood, &Berlin, 1996; Sininger, & Oba, 2001; Cone, 2004). Hence, this cannot serve to confirm the diagnosis of Meniere's disease.

VEMP

VEMP has had a more recent arrival in the field of auditory diagnosis and dating back to studies by Colebatch, Halmagyi and their group of studies that began in 1992. Since then, VEMP has been shown to be useful in diagnosis of several other auditory pathologies. One among these is also Meniere's disease. Individuals with Meniere's disease may have reduced amplitude of VEMP, they may be absent or, paradoxically, their amplitude may be abnormally large occasionally (Young, Huang, & Cheng, 2003).

Young et al. (2003) studied VEMP results in relation to the disease stage. Forty patients with Meniere's disease were considered. Among them six were classified as having stage 1 MD, 12 under stage 2, 17 under stage 3, and 5 patients under stage 4. Results showed that in the stage 1, five of the six patients showed normal VEMPs, and one had augmented VEMPs on the affected side. Among the 12 patients classified as having stage 2 MD, 7 had normal VEMPs, 2 had augmented VEMPs, 4 had decreased VEMPs and 2 had absent VEMPs. Among the 17 with stage 3 MD, VEMPs were normal in 10, decreased in 4, and absent in 3.Among the stage 4 MD, VEMPs were normal in two, decreased in 1, and absent in two. In that study patients at advanced stages more frequently showed absent or decreased VEMPs than patients at earlier stages. The VEMPs were normal in the stage I ears, indicating that the saculocollic reflex retains normal velocity conduction in the earliest stage of MD. Augmented VEMPs was explained as dilatation of the sacular hydrops extending to press against the footplate, this action enhances the

sensitivity of the sacular macula to loud sound. Dilated sacule with an atrophied sacular macula, which was described in one histopathologic study of Meniere's disease, could be an explanation for depressed VEMPs. Absent VEMPs in stage IV disease could result from the sacular wall collapsing onto the otolithic membrane. However, one may be able to notice considerable overlap between the stages in terms of VEMP results. In addition, abnormal asymmetry in VEMP amplitude is the distinctive clinical finding associated with unilateral vestibular dysfunction (Halmagyi, Colebatch &Curthoys, 1994). These findings are not specific only to Meniere's disease; rather they are also observed in other unilateral vestibular pathologies like vestibular neuritis and labyrinthitis (Welgampola& Colebatch, 2005).

Rauch and Steven (2006) reported an elevated VEMP threshold in Meniere's disease (MD) patients and recommended that the threshold be a diagnostic parameter. They also reported a shift of the best frequency of VEMP in MD patients. The best frequency is 500Hz in normal subjects, patients with MD showed less tuning at 500 Hz and shifts of the best frequency to 1000 Hz. However, the number of participants taken in the study was less and more studies need to be done before establishing this test for the diagnosis of Meniere's disease.

Glycerol test

Dehydrating agents such as glycerol or urea can temporarily reverse the effects of endolymphatic hydrops (Meniere's disease) (Angelborg, Klockchoff, &Stahle, 1997). Glycerol in the bloodstream dehydrates the inner ear, improving cochlear function and hearing thresholds (Yellin, Waller & Roland, 1993). Angelborg et al. (1997) recommended an oral dosage of 1.2 ml of glycerol per kg of body weight with the addition of an equal amount of physiological saline.

Glycerol test has been used in conjunction with many tests like Pure tone audiometry (Karjalainen et al., 1977), Speech audiometry (Karjalainen et al., 1977),OAE (Magliulo, Cian, Triches, &Altissimi, 2001), ECochG (Kitaoku, 1994), and VEMP (Ban, Lee, Jin, & Lee, 2007) and has been found to be useful in the diagnosis of Meniere's disease. A 10 dB improvement in two or more adjacent pure tone thresholds and a 12% improvement in speech recognition ability are considered to be highly diagnostic for Meniere's disease using pure tone audiometry (Yellin, Waller,& Roland, 1993). The other tests follow other criteria.

Jablonka, Pospiech, and Orendor (2003) evaluated glycerol test in Meniere's disease with pure tone audiometry and distortion product Otoacoustic emission.The study was done to follow up changes in the pure tone audiometry and DPOAE after glycerol administration in individuals with Meniere's disease. Twenty patients with Meniere's disease and 16 with cochlear hearing loss without vestibular symptoms were subjected to the glycerol test following the complete audiological evaluation. Glycerol was administered orally 1.5 ml/kg of body weight dissolved in the equal amount of the physiological saline. The results of the glycerol test were analyzed with reference to changes in the pure tone threshold and DPOAE amplitude and threshold. The glycerol test was regarded as positive in the audiometry if the pure tone threshold improved at least 15 dB at minimum 3 frequencies. Positive result of the glycerol test in DPOAE was judged if DP amplitude increased more than 5dB at 2 or more frequencies in DP-gram and/or DP threshold lowered at least 10dB in minimum two input output registrations. In the subjects with Meniere's disease, 11 positive and 9 negative glycerol tests in audiometry and 10 positive and 10 negative DPOAE glycerol tests were obtained. In the reference group, one audiometric glycerol test and two DPOAE glycerol tests were regarded as positive. Much conformity, making 85%, between audiometric and DPOAE tests results is observed. The dynamics of the parameter

changing in the consecutive test hours was also similar in both pure tone audiometry and DPOAE.

Mangliulo, Parrotto, Gagliardi, Cuiuli, and Novello (2008) conducted a study in 22 patients with unilateral Meniere's disease. They compared the results of traditional pure tone audiometry glycerol test with that of Vestibular evoked myogenic potential (VEMP) glycerol test and Vestibular evoked periocular potentials (VEPPS). The test was administered both before the administration of glycerol (1.5 g/kg) and 0.5, 1, and 2 hours afterwards. For the traditional pure tone glycerol test, an improvement of at least 10 dB at the lower 2 or 3 frequencies was interpreted as significant. Twelve patients showed unilateral changes in pure tone audiometry after glycerol administration. Four patients showed bilateral involvement with significant improvement only on one side. In the other patients no significant changes were observed on both sides. When the differences between the results of the pre-glycerol and three post-glycerol were more than 20%, the amplitude was considered to be significant. Ten patients from the overall group showed a significant post glycerol increase in amplitude of VEMPs and VEPPs, or both on the affected side. A post-glycerol increase in amplitude of both VEPPs and VEMPs was detected in 5 patients. Two patients showed significant increase in VEPPs and 3 showed significant improvements in VEMPs. They confirmed vestibular evoked potential represents additional diagnostic tool in the diagnosis of endolymphatic hydrops. They also suggested that not only the sacule, but also the utriculus may be involved in the genesis of VEPPs.

Glycerol test in conjunction with other audiovestibular tests appears promising for the diagnosis of Meniere's disease; however the outcome of the glycerol test depends on the pre-test threshold levels. If the hearing loss is mild or moderate, the number of negative test results increase Also, if the degree of hearing loss is severe or more, then the negative results tend to

increase (Karjalainen, 1977). Moreover, the test is associated with unpleasant side effects, including headache, nausea, thirst, diarrhoea and dizziness (Futaki, Kitahara, & Morimoto, 1977). In addition, the testing should be administered in the presence of Otolaryngologist, which is not always possible in most audiological clinics and is also contraindicated in patients with diabetes. With these shortcomings, the test's sensitivity and popularity has reduced and hence does not become the test of choice for the diagnosis of Meniere's disease.

Cochlear Hydrops Analysis Masking Procedure

Cochlear Hydrops Analysis Masking Procedure (CHAMP) is utilised for the diagnosis of Meniere's disease. However, the sensitivity and specificity of CHAMP has been reported to be a subject of controversies in the literature. Don, Kwang, and Tanaka (2005) reported a 100% sensitivity and specificity of CHAMP in identification of Meniere's disease. Lee, Park, Hong, and Kim (2011) reported the sensitivity values to be 85.7% and specificity to be 87.5%.

Contrary to their findings, Ordonez, Rojas, and Hernandez (2009) reported a poorer sensitivity value of 32%. Ordonez et al. (2009) determined the diagnostic value of the cochlear hydrops analysis masking procedure (CHAMP) in patients with definite Meniere's disease. The study was done in subjects with definite Meniere's disease (Group 1), differential diagnosis (Group 2: another audiovestibular diseases or neurologic disorders), and normal hearing (Group 3) were included. One hundred ten cases completed the follow-up, and their results were presented. Sensitivity at 31.3% and specificity at 100% were found in subjects with definite Meniere's disease, features that are more helpful in confirming the diagnosis than in rejecting it. Group 1 showed significantly shorter latency delays than Groups 2 and 3 ($p=0.001$). If definite Meniere's disease is suspected, an abnormal result confirms the diagnosis, however, a normal result does not rule out the Meniere's disease diagnosis. These inconsistencies in the findings

across the studies, leaves a lot to be desired before CHAMP can become 'the test' for the diagnosis of Meniere's disease.

Electrocochleography

Electrocochleography is another of the tests used to diagnose Meniere's disease. ECochG is a variant of auditory brainstem response (ABR) and is a technique of recording synchronous electrical responses of the cochlea and the auditory nerve. It generally involves measurements of the stimulus related cochlear potentials and also includes measurement of the whole nerve or compound action potential of the auditory nerve. The three components of Electrocochleography (ECochG) are cochlear microphonics, summating potential, compound action potential.

The important parameters used are area ratio of Summating Potential to Action Potential (SP/AP) and amplitude ratio of SP/AP. SP/AP is reported to be enlarged in the affected ears of individuals with Meniere's disease (Gibson & Conlon, 1994). Aso, Watanabe, and Mizukoshi(1991) compared ECochG in 29 normal ears, 12 ears with hearing loss of varying etiologies and 16 ears with Meniere's disease. ECochG was performed using transtympanic approach with a reference electrode on the ipsilateral ear lobe and ground on the fore head. Transtympanic electrode consisted of a stainless needle, 0.32mm in diameter and 60 mm in length with epoxy coating expect for the 0.5 mm tip. Results showed that SP/AP is much more useful than SP amplitude for detecting endolymphatic hydrops.A value of 0.3 to 0.4 of SP/AP ratio was considered as the upper limit, where in the study the mean values came around 0.25. There was a significant decrease in SP/AP amplitude in 21 ears following intravenous administration of glycerol. Among 5 Meniere's patients there was a postoperative decrease of

10% or more SP/AP ratio. Ten patients followed 2 years or more and there was no significant change in ECochG and pure tone thresholds.

Other studies have used different cut off values of SP/AP ratio for diagnosis of Meniere's disease and reported the sensitivity values to vary over a wide range between 0.6 and 0.9 across the studies (Mori, Asai, Suizu, Ohta, &Matsunaga, 1985; Mori, Asai, &Matsunaga, 1987; Ferraro &Tibbils, 1999). SP is reported to be present only in 60-65% of normal (Zeng, Ding, McFadden, & Henderson, 1998; Sinha&Vanaja, 2005-06) which would restrict the use of these ratios for diagnosis. The specificity of the SP/AP amplitude ratio in the diagnosis of Meniere's disease has been reported to be 90% or higher (Ferraro, Best, &Arenberg, 1983), the sensitivity of this measurement in the general Meniere's population is only between 55 and 65% or less (Gibson & Conlon, 1994). So this further restricts the usefulness of this technique in the diagnosis of Meniere's disease.

Mori et al. (1987) preformed ECochG and glycerol test on 51 ears of individuals with Meniere's disease. 50% of glycerin was administered in a dose of 2.4ml/kg body weight. A threshold improvement of more than 10dB at two adjacent frequencies was regarded as positive in glycerol test. SP/AP ratio of 0.43 was regarded as positive for Electrocochleography. The positive rate of ECochG and glycerol test was 63 % and 51 %, respectively. The ears with positive result of both tests and of either test were 15 of 51ears (29%) and 43 of 51ears (84%) respectively. The positive rate of ECochG was higher in ears with a moderate to severe hearing loss at high frequencies, while the positive rate of glycerol test was higher in ears with a moderate to severe hearing loss at low frequencies. The study also demonstrated that ECochG is different in selectivity of detection of the endolymphatic hydrops from glycerol test and that the

combination of both tests increases the detection rate of the endolymphatic hydrops in Meniere's disease.

Since there is altered mechanism and movement of the basilar membrane due to increased pressure from the excessive amount of endolymph present in the cochlear duct, there is likelihood of change in the latency difference from one to the other polarity as the pressure would impact one polarity (condensation) more than the other (rarefaction). In a preliminary study by Margolis, Rieks, Fournier, & Levine (1995), the authors reported an increased value of AP latency difference between the condensation and rarefaction polarities in individuals with Meniere's disease. However, the clinical group in the above study was very restricted which warranty a need for this to be explored further.

Saas, Densert, Magnusson, and Whitaker(1998) conducted a study using transtympanic Electrocochleography (TT ECochG) on 30 patients with Meniere's disease, 11 patients with cochlear hearing loss of other aetiologies, and 10 healthy subjects. The latencies of action potential responses to click stimulation were evaluated using alternating polarity clicks, condensation and rarefaction clicks and tone bursts of 1 kHz. The results showed that the latency differences between the condensation and rarefaction click evoked responses were significantly larger in patients with Meniere's disease as compared to patients with other cochlear hearing loss and to healthy subjects. The sensitivity of the TT ECochG, obtained by using measurements of SP/AP ratios and SP amplitude at 1 kHz tone burst stimulation increased from 83 percent to 87 percent by the addition of the condensation- rarefaction shift measurement. The study indicated that the latency shift in the AP response to click evoked stimuli of opposite polarities in TT ECochG could be useful parameter in the detection of suspected endolymphatic hydrops.

However, transtympanic ECochG is not feasible in an audiology clinic as it involves the use of a surgical procedure and the extratympanic counterpart of the same needs to be evaluated.

Chen, Kang, Yeh, and Wang (2004) conducted a study using tympanic electrocochleography (TM ECochG) in 10 normal hearing individuals and 33 individuals with Meniere's disease. The patients with Meniere's disease met the criteria for a definite diagnosis of Meniere's disease defined by the AAO-HNS (1995). They evaluated AP, AP latency shift, SP amplitude, SP/AP ratio using clicks and 1kHz tone burst evoked SP amplitude. The results revealed that the mean AP latency shift was 0.55 ms in the Meniere's disease group and 0.11 ms in the control group. There was a significant increase in the mean AP latency shift in the Meniere's disease group relative to that of the control group. The mean 1 kHz burst-evoked SP amplitude was -0.57 μV in the Meniere's disease group and -0.21 μV in the control group. The mean SP/AP ratio was 0.46 in the Meniere's disease group and 0.22 in the control group. There was no significant difference in the mean 1 kHz burst-evoked SP amplitude or SP/AP ratio of the two groups. They concluded that the AP latency shift may serve as a useful criterion in the detection of Meniere's disease. When measures of AP latency shift and SP/AP click ratio are considered together, ECochG is potentially useful in detecting early cases of Meniere's disease when audiometric abnormality is the only symptom. However, the study used a small number of subjects in the control group.

Chapter- 3

METHOD

The present study was conducted to evaluate the efficacy of latency difference of action potential between rarefaction and condensation polarities in the diagnosis of Meniere's disease. This was aimed at specifically using extratympanic recording technique of ECochG for the same.

Subject selection criteria

The study incorporated three sets of participants which were divided into three groups; a Meniere's disease group, sensorineural hearing loss group and a group of healthy individuals. Group I consisted of 21 ears of participants in the age range of 18-55 years (9 males & 12 females) who were diagnosed with endolymphatic hydrops based on the questionnaire of American Academy of Otolaryngology Head and Neck Surgery (1995). Each of the participants within this group had pure tone average threshold of less than 55 dB HL. Their unaffected ears served as a separate group for a number of analyses. The group II consisted of 25 ears of 16 participants (7males &9 females) with sensorineural hearing loss (other than Meniere's disease) in the same age range as group I. The other subject selection criteria for this group included exclusion of individuals with pure-tone average threshold exceeding 55 dBHL and sloping audiometric configuration. The existence of neural pathology was screened out using auditory brainstem response (ABR). Forty eight ears of healthy individuals (age & gender matched to group I) with normal audio-vestibular system served as the participants in group III.

Instrumentation

A calibrated diagnostic audiometer GSI-61 with TDH-39 supra-aural headphones housed in MX-41/AR ear-cushions and Radioear B-71 bone vibrator was used for estimating air conduction and bone conduction thresholds. The same set of equipments in AC mode alone was used for speech audiometry.

A calibrated diagnostic immittance meter GSI-Tympstar was used to obtain Tympanogram. Same equipment was also used for obtaining ipsilateral and contralateral acoustic reflex thresholds (ARTs).

An Intelligent Hearing System Smart EP version 4.0 with ER-3A insert earphones connected with TIPtrode was used to acquire extratympanic ECochG. The same instrument without TIPtrode was used to acquire ABR.

Procedure

The routine audiological evaluation involved pure tone audiometry, speech audiometry, and immittance evaluation. Pure tone audiometry was done using the Carhart and Jerger (1959) modified Hughson and Westlake method for the octave frequencies of 250 through 8000 Hz for air conducted stimuli using TDH-39 head phones. Bone conduction thresholds were obtained for the octave frequencies of 250 through 4000 Hz. The word recognition score (WRS) were obtained at the most comfortable level (MCL) using the standardized word lists in the client's native language. Immittance evaluation was done to rule out any middle ear pathologies. It involved obtaining tympanogram and acoustic reflex thresholds (both ipsilateral and contralateral). Tympanograms were obtained using a 226 Hz probe tone frequency whereas the

ARTs were obtained at frequencies from 500 Hz through 4000 Hz using the above mentioned probe tone frequency. The ABR was used to screen out neural pathology.

ECochG was administered by seating the subjects comfortably in a well illuminated acoustically treated test room with the ambient noise levels within ANSI specifications (ANSI S3.1-1999). The skin overlying the electrode sites were cleaned using Nuprep skin preparing gel prior to the electrode placement. For the preparation of ear canal skin, the same skin preparing gel was used with a swab stick.The electrodes were mounted using Ten20 conduction gel and surgical plaster. The electrode montage consisted of TIPtrode as the non-inverting electrode which was placed in the ear canal; inverting electrode was placed on the test ear mastoid; and ground was placed on the forehead. The inverting and ground electrodes were the regular disc type silver chloride electrodes. An adult-size TIPtrode was attached to insertion cushion on the TIPtrode tubing. Tiptrode plug was then compressed tightly and placed in the ear canal while pulling the pinna upward, backward, and slightly outward, in a circular movement. It was ensured that the impedance for each electrode was less than 5KΩ and the inter-electrode impedance difference was less than 2 KΩ. The protocol for ECochG has been shown in table 3.1.

ABR was administered with the electrode montage that included the placement of inverting electrode on the test ear mastoid, non-inverting electrode on the forehead and ground on the non-test ear mastoid. All the electrodes were the regular disc type silver chloride electrodes. The participant preparation and the impedance values required for the electrodes for ABR were similar to that of ECochG. The protocol for ABR has been shown in table 3.1.

Table 3.1:

Protocol for recording ECochG and ABR.

Stimulus parameter	ECochG	ABR	Acquisition parameter	ECochG	ABR
Stimulus intensity	90 dB nHL	90 dB nHL	Analysis time	5ms	10 ms
Stimulus rate	11.1/s	11.1/s	Pre-stimulus time	2ms	0 ms
Stimulus polarity	Rarefaction and condensation	Rarefaction and condensation	Amplification	50000 times	100000 times
Stimulus polarity	Clicks	Clicks	Filter settings	10 Hz - 3000	100 Hz-3000 Hz
			Sweeps	1000	1000

NOTE: ECOchG – Electrocochleography; ABR – Auditory brainstem response; Hz – Hertz.

Measure

The latency of the action potential and wave I of ABR for rarefaction and condensation, and SP/AP ratio were measured for all the group of participants. From that the shift in the latencies between the condensation and rarefaction polarities were measured by subtracting one from the other.

Statistical analysis

A descriptive statistics was done to obtain the mean and standard deviation for the measures.Since the data obtained was non-normally distributed, the non-parametric statistical

analysis was done. This involved a Kruskal Wallis test for overall comparison and a Mann-Whitney U test for pairwise comparison. A Kappa analysis was also done for checking the agreement between the SP/AP ratio and AP latency difference between the condensation and rarefaction polarities of click.

Chapter- 4

RESULTS

The present study was conducted with the aim of checking the utility of latency difference between the condensation and rarefaction polarity of action potential in the diagnosis of Meniere's disease. In addition, it was aimed at evaluating the utility of a similar difference for ABR wave I in the diagnosis of Meniere's disease. Furthermore, the study also aimed at checking the efficacy of SP/AP ratio in the diagnosis of Meniere's disease and comparing this method to the AP latency difference to find out which is a better tool for the diagnosis of Meniere's disease. To fulfil these aims, the participants were divided in to 3 groups. The results are discussed under the headings of action potential (AP) latency difference, SP/AP ratio, and ABR latency difference to compare between groups. Also a correlation between SP/AP ratio, ABR latency difference, and AP latency difference was evaluated. For several comparisons, the unaffected ears of individuals with Meniere's disease were considered as a separate group.

4.1AP latency difference between condensation and rarefaction polarities of ECochG

All the participants within each of the three groups underwent Electrocochleography and the action potentials were identified in the condensation as well as the rarefaction polarities' waveforms. Sample ECochG waveforms from one participant from each of the groups are shown in *figure 4.1.1*.

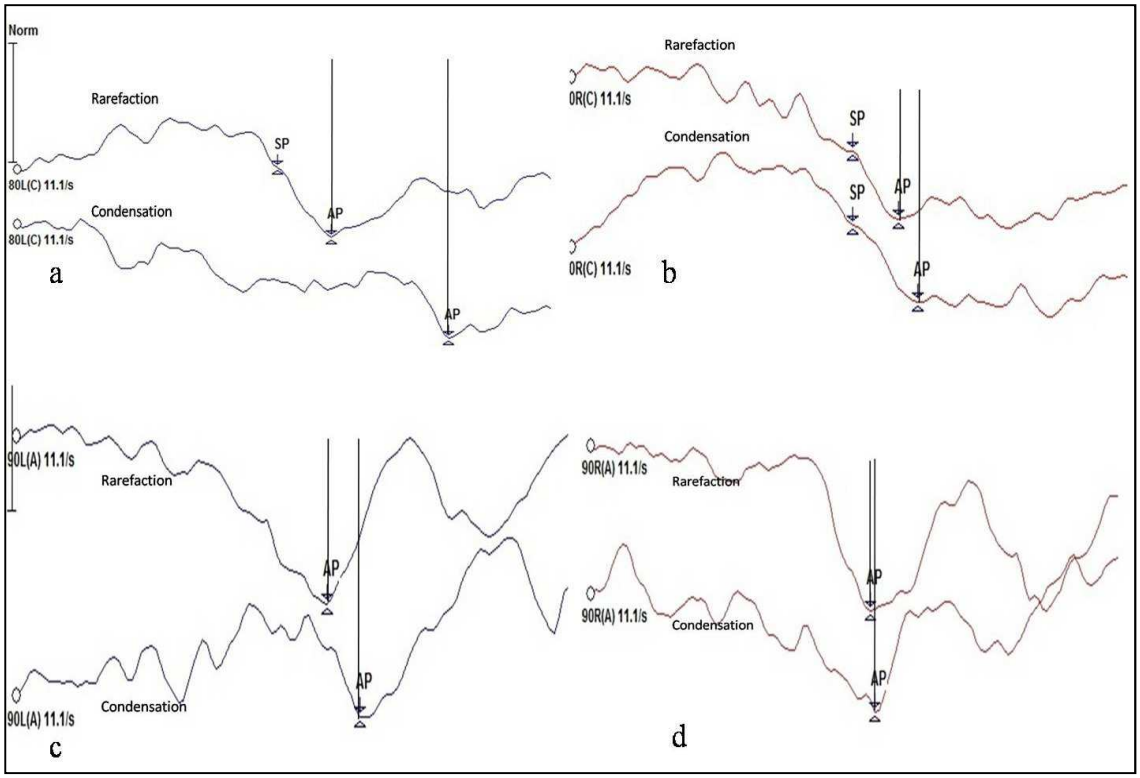

Figure 4.1.1: Representative AP waveforms (in alphabetic order) from affected ears with Meniere's disease, ears of healthy individuals, unaffected ears of individuals with Meniere's disease, and ears with sensorineural hearing loss.

Statistical analysis was done using Statistical Prediction for the Social Sciences (SPSS) software version 17. The waveforms were analyzed for latencies of action potential for rarefaction and condensation polarities and the difference between the two was obtained. The values so obtained were then subjected to *descriptive analysis* to obtain mean and standard deviations. The *mean* and *standard deviation* values for ears of healthy individuals, ears of individuals with sensorineural hearing loss, unaffected ears of individuals with Meniere's disease and affected ears of individuals with Meniere's disease were found to be *0.13 ms (S.D = 0.02), 0.13 ms (S.D = 0.02), 0.21ms (S.D = 0.02),* and *0.47ms (S.D = 0.11)* respectively. The mean of AP latency difference in the affected ears of individuals with Meniere's disease was higher than the other two groups and also compared to their own unaffected ears.Likewise, the unaffected ears of individuals with Meniere's disease also produced larger mean latency difference value

than the ears of healthy individuals and also those of the individuals with sensorineural hearing loss. The same has been depicted in figure 4.1.2.

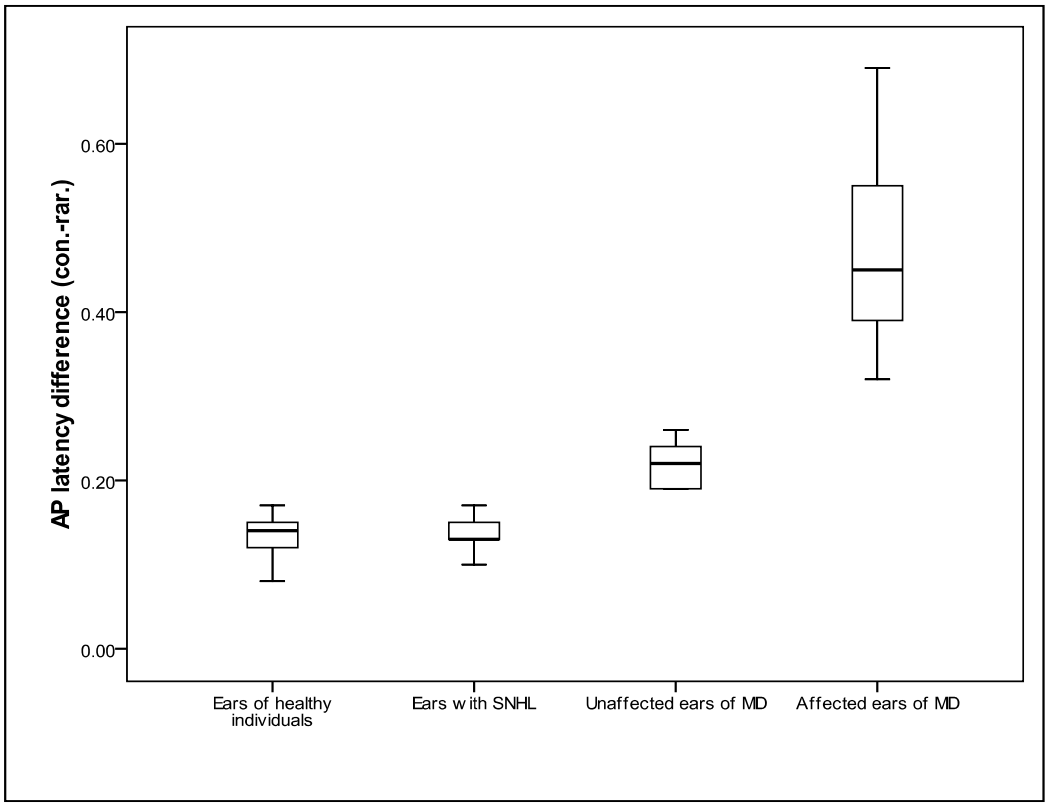

Figure 4.1.2: The box plot of AP latency difference between condensation and rarefaction polarities.

A *Kruskal Wallis test* was administered to compare between the ears of healthy individuals, ears with SNHL, unaffected ears of individuals with Meniere's disease and affected ears of individuals with Meniere's disease in terms of the difference between the Action potential latencies between rarefaction and condensation clicks. The results revealed *significant difference* between the latencies of the two polarities $[\chi^2(3) = 71.889, p = 0.000]$. A *post hoc analysis* was done using *Mann-Whitney U test* for pair wise comparison between all possible pairs. The pair wise comparison revealed a *significant difference* between all the pairs except between ears of healthy individuals and ears with SNHL. The latency difference between the polarities in the

affected ears of individuals with Meniere's disease was also significantly different from the othergroups. The latency difference was largest for the affected ears of individuals with Meniere's disease followed by their unaffected ears. The ears of healthy individuals and those of individuals with sensorineural hearing loss revealed lesser latency difference between the polarities than either of the above two and the two were comparable. The exact *'p'* and *'Z'* values are given in table 4.1.1.

Table 4.1.1.
'Z' and 'p' values of Mann-Whitney U test for AP latency difference between condensation and rarefaction polarities.

	Ears of healthy individuals	Ears of SNHL	Unaffected ears of MD	Affected ears of MD
Ears of SNHL	Z = -0.653		Z = -5.805	Z = -4.968
	p = 0.514		p = 0.000	p = 0.000
Unaffected ears of MD	Z = -5.530			Z = -4.843
	p = 0.000			p = 0.000
Affected ears of MD	Z = -6.601			
	p = 0.000			

NOTE: SNHL – Sensorineural hearing loss; M.D – Meniere's disease.

4.2 ABR wave I latency difference between condensation and rarefaction

All the participants within each of the groups underwent ABR and peaks (waves) were identified. Sample ABR waveforms from one participant from each of the groups are shown in *figure 4.2*.1

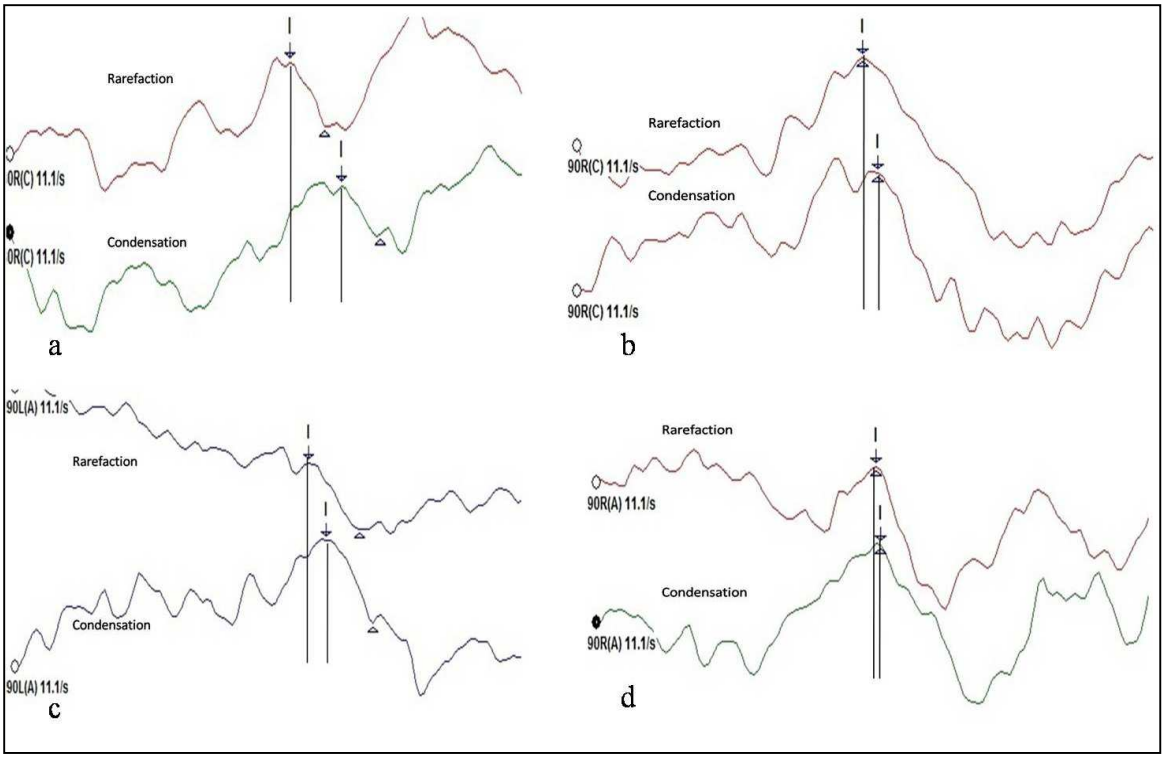

Figure 4.2.1: Panel 'a', 'b', 'c' and 'd' represent the ABR waveforms obtained from ears of individuals with Meniere's disease, ears of healthy individuals, unaffected ears of individuals with Meniere's disease, and ears with sensorineural hearing loss respectively.

The waveforms were analyzed for latencies of wave I of ABR for rarefaction and condensation polarities and the difference between the two was obtained. The values thus obtained were then subjected to descriptive analysis. The ears of healthy individuals produced a *mean* ABR wave I latency difference of *0.08 ms (S.D. = 0.03)* between the two polarities used in the study. The difference for ears with sensorineural hearing loss, unaffected ears of Meniere's disease, and affected ears of Meniere's disease was *0.08 ms (S.D = 0.03), 0.13ms (S.D = 0.02),* and *0.32ms (S.D = 0.07)* respectively. A graphical illustration of the same has been put forward in figure 4.2.2.

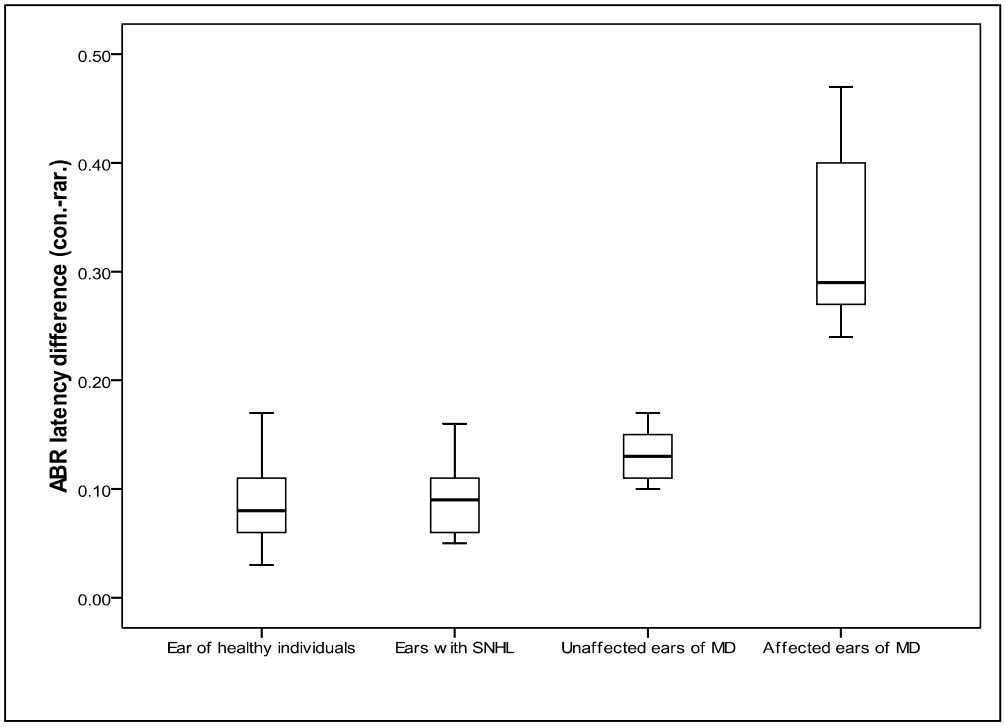

Figure 4.2.2: The box plot of the of ABR latency difference between condensation and rarefaction polarities.

A *Kruskal Wallis test* was administered to compare the groups in terms of the latency difference between rarefaction and condensation polarities for wave I of ABR. The results revealed *a significant difference* between the groups *[$\chi^2(3) = 60.358$, $p = 0.000$]*. A pair wise comparison was done using the *Mann-Whitney U test statistic* which revealed the latency difference of ABR between the polarities in the affected ears of individuals with Meniere's disease to be *significantly different* from all of the groups (ears of healthy individuals, ears with SNHL, & unaffected ears of individuals with Meniere's disease). The comparison between ears of healthy individuals and those of sensorineural hearing loss showed *no significant difference*. The latency difference between the polarities in the unaffected ears of individuals with Meniere's disease was*significantly different* from all others. The latency difference was greatest for the affected ears of Meniere's followed by their unaffected ears. The other two groups produced

nearly equivalent latency differences. The 'Z' and 'p' values for the pairwise comparisons also have been shown in table 4.2.1.

Table 4.1.1.
'Z' and 'p' values of Mann- Whitney U test for ABR latency difference between condensation and rarefaction polarities.

	Ears of healthy individuals	Ears of SNHL	Unaffected ears of MD	Affected ears of MD
Ears of SNHL	Z = -0.579		Z = -3.415	Z = -5.798
	p = 0.563		p = 0.001	p = 0.000
Unaffected ears of MD	Z = -3.749			Z = -4.844
	p = 0.000			p = 0.000
Affected ears of MD	Z = -6.588			
	p = 0.000			

NOTE: SNHL – Sensorineural hearing loss; M.D – Meniere's disease.

4.3 SP/ AP ratio

The ECochG waveforms obtained from each individual were analyzed. The SP/AP amplitudes were obtained and their ratio was computed and subjected to *descriptive analysis*. The SP/AP amplitude ratio was highest for the affected ears of individuals with Meniere's disease *[Mean = 0.43, S.D = 0.19]*. The ears with sensorineural hearing loss *[Mean = 0.26, S.D = 0.07]* produced comparable SP/AP ratio values to the ears of healthy individuals *[Mean = 0.26, S.D = 0.07]* and also the unaffected ears of Meniere's disease *[Mean = 0.26, S.D = 0.07]*. A graphical representation of the same has been provided in figure 4.3.*1*.

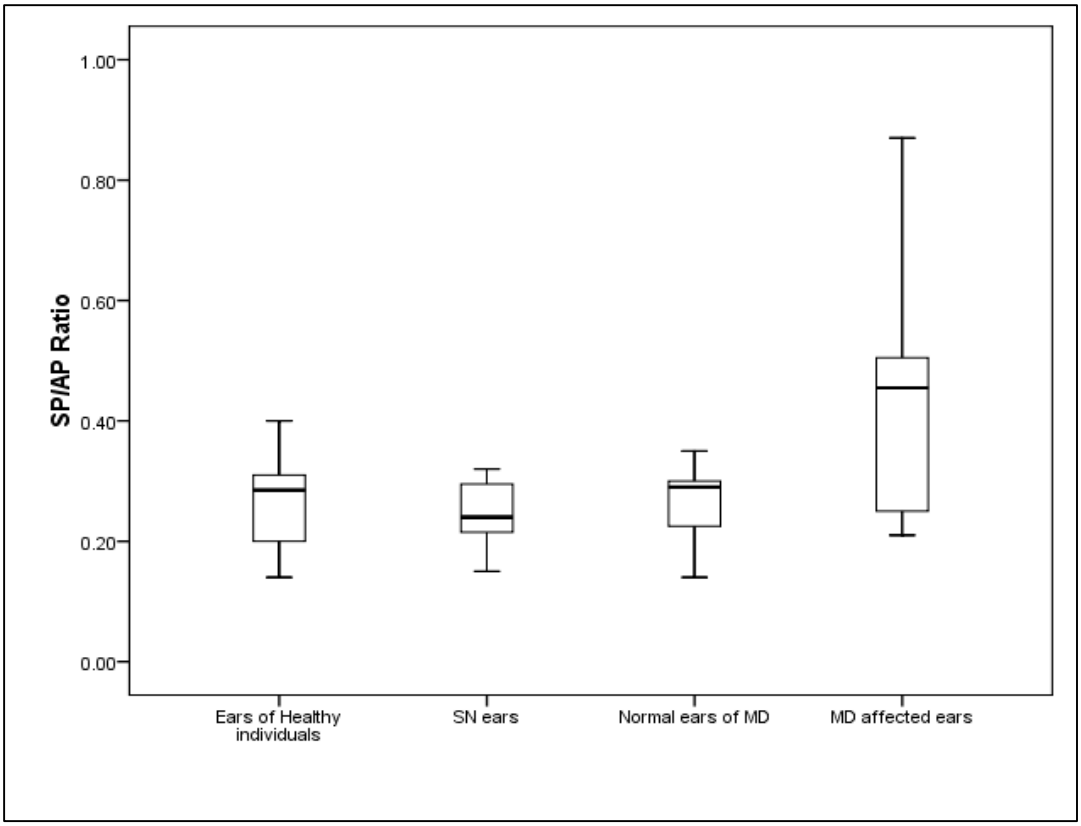

Figure 4.3.1: The box plot of the SP/AP amplitude ratio.

A *Kruskal Wallis test* was administered to compare the four groups in terms of SP/AP ratio. The results revealed a *significant difference* in SP/AP amplitude ratio between the groups *[$\chi^2(3) = 11.31$, $p = 0.01$]*. A *post hoc analysis* was done using *Mann-Whitney U test* for pair wise comparison between all possible pairs. The affected ears of Meniere's disease were found to be *significantly different* from all others on the pair wise comparison. This apart, there was *no significant difference* between other pairs. The *'p'* and *'Z'* values of pairwise comparison have been given in table 4. 3.1

Table 4.3.1
Z' and 'p' values of Mann- Whitney U test of SP/AP ratio.

	Ears of healthy individuals	Ears of SNHL	Unaffected ears of MD	Affected ears of MD
Ears of SNHL	Z = -6.14		Z = -0.45	Z = - 2.314
	p = 0.53		p = 0.653	p = 0.021
Unaffected ears of MD	Z = -0.77			Z = -2.147
	p = 0.93			p = 0.032
Affected ears of MD	Z = - 2.991			
	p = 0.003			

NOTE: SNHL – Sensorineural hearing loss; M.D – Meniere's disease.

4.4 Relationship between AP latency difference and SP/AP ratio in the affected ears of the individuals with Meniere's disease

The present study aimed at evaluating a relationship between AP latency difference and SP/AP ratio in individuals with Meniere's disease. The *Spearman's correlation analysis* was used to obtain the relationship between the difference in AP latencies in rarefaction and condensation polarities and SP/AP ratio in the affected ear of MD. The results showed the existence of *slight negative correlation* (Viera& Garrett, 2005) between the two which was statistically *not significant*[r_s= *-0.070, p = 0.797]*. Figure 4.4.1 shows the scatter plot illustrating this relationship.

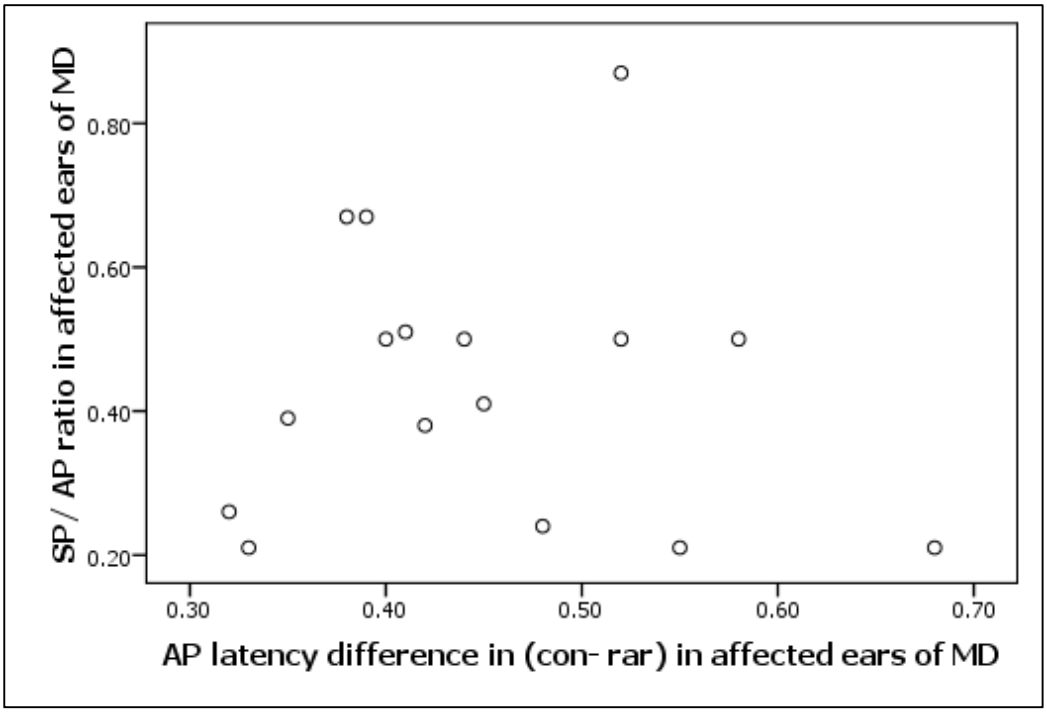

Figure 4.4.1: The scatter plot showing the relationship between SP/AP ratio and AP latency difference in the affected ears of individuals with Meniere's disease.

Another statistical tool used was the *Kappa coefficient analysis*. For this, the AP latency difference values were converted into categorical data of Meniere's and non-Meniere's disease ears by using the mean reference values from the available research regarding the two variables. The mean value of AP latency difference of ≥ *0.40*ms (Orchik, Ge, Shea, 1998) and SP/AP ratio of ≥ *0.35* (Ohashi, Nishino, Arai, Hyodo, & Takatsu, 2009) was used to categorize the data into Meniere's and Non-Meniere's ears. The SP was present in only 16 ears (out of 21 ears) of the individuals with Meniere's disease and hence *Kappa correlation analysis* was done using only these many ears. The results revealed *slight correlation* (Viera& Garrett, 2005) which was statistically *not significant [K =0.127, p =0.61]*. There was agreement for positive results of Meniere's disease for 7 ears (out of 16) and negative results for 2 ears. The overall agreement between tests for Meniere's disease diagnosis was only 56.25%. This implies that a correct diagnosis of Meniere's disease versus non-Meniere's disease was made in only 56.25% of

individuals when using a positive criterion on both the methods. When the diagnosis of MD was based on the positive results on either of the two methods, the identification of MD increased to 85%.

4.5 Relationship between ABR wave I latency and SP/AP ratio in the affected ears of individuals with Meniere's disease.

One of the objectives of the study was to check if the ABR wave I latency difference between condensation and rarefaction polarities could yield results that could help in the diagnosis of Meniere's disease. A *Spearman's correlation analysis* was used to correlate the difference in ABR wave I latencies and SP/AP ratio in the affected ear of individual with MD. The results showed *slight negative correlation* (Viera& Garrett, 2005) between the two which was statistically *not significant* [r_s=*-0.131,p = 0.630]*. The same has been illustrated in figure 4.5.1.

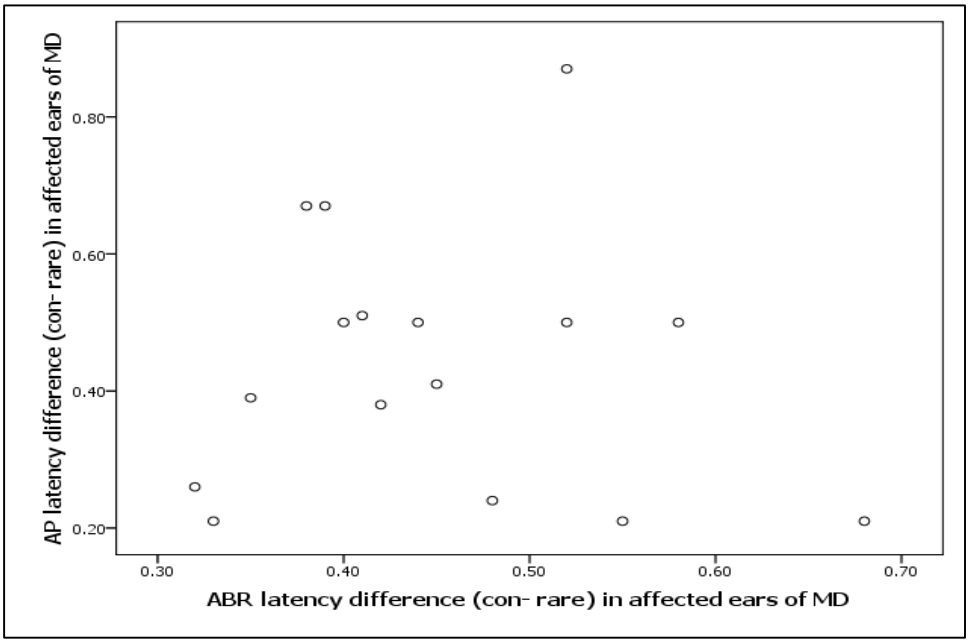

Figure 4.5.1: The scatter plot showing the correlation between SP/AP ratio and ABR wave I latency difference in the affected ears of individuals with Meniere's disease.

4.6 Relationship between AP latency difference and ABR wave I latency difference in the affected ears of individuals with Meniere's disease

A *Spearman's correlation analysis* was used to establish the relationship between the difference in AP latencies and ABR wave I latencies in the affected ears of individuals with Meniere's disease. The results revealed an *almost perfect positive correlation* (Viera& Garrett, 2005) between the two set of variables, and this was statistically *significant* [r_s= *0.938, p = 0.000]*. The same has been illustrated in figure 4.6.1.

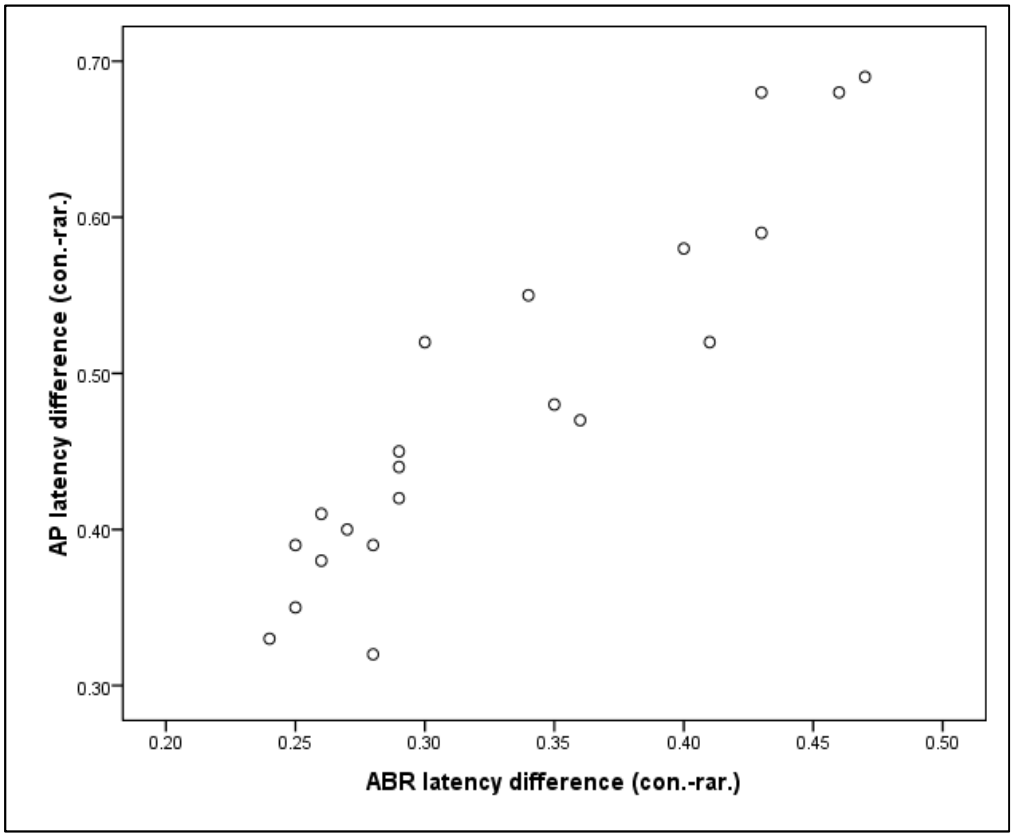

Figure 4.6.1: The scatter plot showing the relationship between AP latency difference and ABR wave I latency difference in the affected ears of individuals with Meniere's disease.

To summarize, the results of the present study indicated that the AP latency difference in the affected ears of individuals with Meniere's disease was *higher* than their own affected ears as well as the ears with sensorineural hearing loss and ears of healthy individuals. Compared to the

ears with sensorineural hearing loss and the ears of healthy individuals, the unaffected ears of individuals with Meniere's disease produced *significantly larger* latency difference between the polarities for AP. The ears of healthy individuals and those of individuals with sensorineural hearing loss revealed comparable values. A similar trend to AP was also observed for the wave I of ABR for the difference between the two polarities. The affected and unaffected ears of individuals with Meniere's disease produced *significantly larger* latency differences for ABR wave I than the ears of healthy individuals and those with sensorineural hearing loss. The comparison between the affected and the unaffected ears of individuals with Meniere's disease revealed a *significantly* larger latency difference for the affected ear. It was also observed that the SP/AP ratio was *highest* for the ears of individuals with Meniere's disease. All the other groups revealed comparable SP/AP ratio values.In the affected ears of individuals with Meniere's disease, there was *no correlation* between the AP latency difference and SP/AP ratio, and also between ABR wave I latency and SP/AP ratio. However, the latency difference between the polarities of ABR wave I was *highly* and *positively correlated* with the latency difference between the polarities of AP.

Chapter-5

DISCUSSION

5.1AP latency difference between condensation and rarefaction polarities of ECochG.

From the results of the present study it was evident that the mean AP latency difference between condensation and rarefaction polarities of APwas higher for the affected ears of the individuals with Meniere's disease compared to ears of healthy individuals, ears with sensorineural hearing loss and also their own unaffected ears. The present study did not compare the rarefaction and condensation polarities separately across the groups. However, the findings in literature have shown the difference to be prominent for condensation polarity (Saas et al., 1998). The authors reported no difference for rarefaction polarity between the healthy individuals, individuals with sensorineural hearing loss and those with Meniere's disease; however the individuals with Meniere's disease revealed longer latency of AP for condensation polarity than the other two groups of their study. This probably may be the reason for the larger difference between the latencies of the two polarities in individuals with Meniere's disease even in the present study. The prolongation of latency for condensation clicks alone may be explained on the basis of postulations of Tonndorf (1975) and the impact of hydrops on the travelling wave velocity (Eggermont&Odenthal, 1974). Tonndorf(1975), through his cochlear model, postulated that the basilar membrane, when loaded with endolymphatic hydrops, undergoes a downward displacement. Eggermontet al. (1974) studied the mode of the excitation in human cochlea and demonstrated that the latency of the AP was dependent on the velocity of the travelling wave, especially in cases with endolymphatic hydrops. The travelling wave was more affected in response to a condensation clicks than to rarefaction clicks due to the load of endolymphatic hydrops, and this resulted in a latency prolongation for condensation polarity. Therefore, the

increased stiffness and change in position of the basilar membrane is likely to influencethe pattern ofthe travelling wave motion, thereby aiding the explanation of the increased latency difference between the polarities in the individuals with Meniere's disease.

The results of the present study are in agreementwith the findings in the literature about the AP latency difference in Meniere's disease. Sass et al. (1998) conducted a study usingtranstympanic electrode placement on 30 individuals with Meniere's disease whose pure tone average thresholds ranged between 20 and 65dB. In addition, their study also used 11 patients with cochlear hearing loss of other aetiologies with pure tone average ranging between 30 and 60 dB and also 10 healthy subjects. They reported a mean difference in AP latencies between condensation and rarefaction of 0.02ms, 0.01ms, and 0.32ms respectively in ears of healthy individuals, ears with sensorineural hearing loss, and ears of individuals with Meniere's disease.The findings of the present study revealed a similar pattern across the groups. However, the values obtained were higher (0.13 ms, 0.13 ms, and 0.47 ms in the same order as above). The values observed in the present study were appreciably higher for all the three groups of Sass et al. (1998). The differences in the values between the present study and Saas et al. (1998) could be related to the differences in the site of electrode placement. They used a transtympanic (near field) placement of the non-inverting electrode as against the extratympanic (far field) placement in the present study. Another study by Chen, Kang, Yeh, and Wang (2004) used extratympanic electrode placement on ears of 10 healthy individuals and 33 individuals with Meniere's disease. They obtained a mean AP latency shift of 0.55 ms in the ears of individuals Meniere's disease and 0.11 ms in the ears of healthy individuals. The values observed in the present study were similar to those reported by Chen et al. which probably may be related to the use of similar method, including the extratympanic electrode placement in both the studies. So it could be

concluded that the latency difference of AP between the polarities is greater in individuals with Meniere's disease irrespective of the site of electrode placement generally used for ECochG recordings. However, the cut-off values for Meniere's disease diagnosis could vary depending on the site of placement of electrodes. This calls for obtaining separate clinical values for different electrode placements for the diagnosis of Meniere's disease using ECochG.

The study revealed another finding of interest. The unaffected ears of individuals with Meniere's disease showed significant deviation in terms of latency difference between the polarities from the ears with sensorineural hearing loss and those with healthy individuals. The latency difference was*significantly* larger for the unaffected ears of individuals with Meniere's disease than their healthy and sensorineural counterparts. The findings in the literature has shown that, though Meniere's disease generally begins as a unilateral condition, it has a tendency to progress to the other ear within 2-7 years of its onset in the first ear in more than 50% of the individuals (Morrison, 1981., Salvinelli, Trivelli, Greco, Silvestrini, Fernandez, &Pallini, 1998; Jackson & Silverstein, 2002., Saeed& Penny, 2011). Similar views were echoed by Huffelen et al. (1998) who obtained smaller OAE amplitudes in unaffected ears of individuals with Meniere's disease than the ears of normal hearing adults. They attributed this to the early manifestation of bilateral Meniere's disease. The findings in the present study also showed a similar trend, though for AP. The findings of the present studyindicate that the latency difference of AP between the polarities could be useful in the early detection of onset of bilateral Meniere's in the individuals who are already suffering from the unilateral condition.

5.2 ABR wave I latency difference between condensation and rarefaction.

The results of the present study indicated towards a greater difference in Meniere's disease in terms of the latency difference between condensation and rarefaction click-evoked wave I of ABR. Tietze and Pantev (1986) reported a mean difference of 0.06 ms in ABR wave I latency between condensation and rarefaction polarities in normal hearing individuals. For high-level clicks, the wave I (Coats& Martin, 1977) or eighth nerve action potential (Peake& Kiang, 1962) has been reported to be approximately 0.2 ms earlier for rarefaction than for condensation stimuli. Contrary to this, Beattie (1988) found no significant differences between the latencies for human wave I elicited by rarefaction and condensation clicks. The findings of the present study are in agreement with those of Coats et al. (1977) and in disagreement with Beattie (1988). However, these values were very small and the test-retest reliability of up to 0.3 ms has been reported (Hall, 2007) for different waves, including wave I of ABR. Thus such small deviations in normals could be ignored. The absence of or very small phase-related latency difference is expected for normal-hearing subjects because the normal click-evoked ABR is dominated by high-frequency neural responses (Don &Eggermont, 1978), which are not significantly affected by stimulus phase. However in the ears with Meniere's disease, the changes due to endolymphatic hydrops has been documented to result in prolongation of AP for condensation polarity, thereby by increasing the latency difference of AP between the two polarities (Saas et al., 1998; Chen et al., 2004). Since the wave I of ABR corresponds to the AP (Moller et al., 1983; Hall &Antonelli, 2001), a similar prolongation of latency for condensation polarity is justified. However, the present study is one of the first that has used ABR for the diagnosis of Meniere's disease and there are no other studies that reported about the usefulness of ABR in the diagnosis of Meniere's disease.

The present study also revealed another intriguing finding. The unaffected ears of individuals with Meniere's disease revealed significantly larger difference between the latency of wave I of ABR between the polarities compared to the ears of healthy individuals and the ears with sensorineural hearing loss. This may be an early sign of progression of the disease to the unaffected ear in the individuals with unilateral Meniere's disease. There are a number of studies that have reported a tendency of Meniere's disease to progress to the other ear within 2-7 years of its onset in the first in more than 50% of the cases (Morrison, 1981; Salvinelli et al., 1998; Jackson et al., 2002; Saeed& Penny, 2004). But there are no studies that have used ABR wave I latency difference between the polarities and demonstrated such a finding. However, the reports using OAEs have shown that the unaffected ears of individuals with Meniere's disease had significantly lower amplitudes and the authors discussed this as an early sign of progression to bilateral condition (Huffelen et al., 1998). On similar lines the findings of present study may be considered an early sign for progression to bilateral Meniere's disease. So the present study shows that the technique of latency difference between condensation and rarefaction not only aids the diagnosis of Meniere's disease in the affected ears but also is capable of predicting its spread in the unaffected ear.

5.3 SP/ AP ratio.

The mean SP/AP amplitude ratios in the affected ears of individuals with Meniere's disease was higher when compared to ears of healthy individuals, ears of individuals with sensorineural hearing loss, and also the unaffected ears of individuals with Meniere's disease in the present study. The mean SP/AP ratios in these were 0.26, 0.24, 0.26, and 0.43 respectively. Similar patterns of findings have been reported in literature about SP/AP ratio (Mori et al., 1987; Chen et al., 2004). Mori et al. (1987) conducted a study in which they found the mean SP/AP

ratio of 0.22, 0.20, and 0.63 respectively in ears of healthy individuals, ears of individuals with sensorineural hearing loss, and ears with Meniere's disease. Chen et al. (2004) obtained a mean SP/AP ratio of 0.46 in the individuals with Meniere's disease and 0.22 in the ears of healthy individuals. The differences between the ratio values observed in the present study and that by Mori et al., (1987) may be because of the differences in the method and also the presence of a higher variability within the group with Meniere's disease in terms of higher standard deviation for the Meniere's group in their study. The present study used Tiptrode placed at the entrance of the ear canal as the non-inverting electrode as against silver ball electrode placed near the tympanic membrane at a distance of 3 mm in the study by Mori et al. (1987). Also, the standard deviation obtained was 0.19 in the present study as opposed to 0.44 in Mori et al.(1987). Furthermore, the volatile nature of the Meniere's disease itself, which causes high variability in the test results usually, may have contributed to the differences between their study and the present study. However, Chen et al. (2004) used the same electrode placement (extratympanic) as the present study and obtained a mean SP/AP ratio of 0.46 in Meniere's disease and 0.22 in normal hearing individuals. These findings are similar to the ones observed in the present study and thusit probably extends further support to reasons of the differences observed between the present study and the study by Mori et al. (1987).

5.4 Relationship between AP latency difference and SP/AP ratio in the affected ears of the individuals with Meniere's disease.

The present study revealed the existence of *no significant* correlation between AP latency difference and SP/AP ratio. Similar findings have also been reported by Ohashi, Nishino, Arai, Hyodo, and Takatsu (2009). This disagreement between the techniques may be attributed to the differences in the physiology of the AP and SP generation. The AP waveform is characterized by

a series of brief, predominantly negative peaks representing the distribution of underlying neural firings. The response to moderately intense stimulation tends to be dominated by neural contributions from the basal or high frequency end of the cochlea (Kiang, 1965), at least in normal ears and pathologic ears no worse than moderate hearing loss. The AP magnitude can also be viewed as a reflection of inner hair cell output. The SP is a complex response made up of several components. It reflects the displacement time pattern of cochlear partition. The SP is stimulus related and generated by the hair cells of the organ of Corti(Dallos, 1973).The SP manifests itself as a shift in the CM baseline, the direction of which is indicated and dictated by an interactive effect between stimulus parameters and the location of the recording electrode (Dallos, 1973). In general, the ECochG waveform recorded from patients with suspected endolymphatic hydrops is often characterized by an enhanced summating potential (Ferraro, Arenberg, &Hassanein, 1985).Therationale usually given for this finding is that an increase in endolymph volume alters the hydromechanicalcharacteristics of the inner ear because of the resultant increase in intra-labyrinthine pressure. When this occurs, the normal vibratory asymmetry of the basilar membrane is augmented. Since the SP supposedly reflects this vibratory asymmetry, it too will be enhanced during a hydropic state. However, AP has a distinctly different physiology and hence the presentation in a hydropic pathology may accordingly be different. This probably may explain the disagreement between the two techniques for the diagnosis of MD and calls for further studies to clarify the reasons.

In the present study the agreement between the two measures was found only for 9 ears. This implied that a Meniere's disease versus non-Meniere's disease diagnosis was appropriately made in only 56.25 % of the individuals when using a criterion of positive results on both techniques. However, when the criterion was changed to positive result on either of the two, 85

% of the cases were diagnosed as Meniere's disease. So both these techniques should be used in the protocol for the diagnosis of Meniere's disease as the two are likely to give complementary information, thereby supplementing in the diagnosis. It might be interesting to note if there would be a correlation between the agreement of the two tests and the stage of the Meniere's disease diagnosed as per AAO-HNS, (1995). However, due to smaller sample size, a correlation of this kind could not be taken up. This may be considered in future studies using the two techniques and if found to correlate, it could well become an objective way of staging Meniere's disease.

5.5 Relationship between ABR wave I latency difference and SP/AP ratio in the affected ears of the individuals with Meniere's disease.

The results of the present study revealed a lack of relationship between ABR wave I latency difference and SP/AP ratio in the affected ears of the individuals with Meniere's disease. Lack of agreement may be due to the differences in the physiology of generation of wave I of ABR and SP. Wave I of ABR is generated at the distal part of the auditory nerve (Wada & Starr, 1983) whereas SP is generated from the hair cells in the cochlea (Dallos, 1973). The two are likely to represent different aspects of physiology owing to these different structures (hair cells versus nerve fibers) involvement. Further, there are no such studies in the literature that compare latency difference between the two polarities for wave I of ABR and SP/AP in individuals with Meniere's disease. Present study is one of the first of this kind and the findings indicate towards a lack of correlation between this technique and the more established SP/AP amplitude ratio in the diagnosis of Meniere's disease. However, wave I of ABR has been reported to correspond to AP of ECochG (Moller et al., 1983; Hall et al., 2001) and a similar lack of correlation of AP with SP/AP ratio (Ohashi et al., 2009) could explain the results of the lack of correlation so found.

5.6 Relationship between AP latency difference and ABR wave I latency difference in the affected ears of individuals with Meniere's disease

The present study indicated a *strong correlation* between AP latency difference and ABR wave I latency difference in the affected ears of individuals with Meniere's disease. Tonndorf (1975), through his cochlear model,postulated that the basilar membraneundergoes a downward displacement when loaded with an excessive amount of endolymph. Distortion at the level of the basilar membrane will generally be reflected at the auditory nerve fibers in terms of the neural responses. Since wave I of ABR reflects the activity in the distal portion of the auditory nerve (Wada & Starr, 1983) and also corresponds to AP (Moller et al., 1983, Hall et al., 2001), the finding of a strong correlation is expected and justified.There are no such studies in the literature that comparethe latency difference of wave I of ABR and AP latency difference between the two polarities. So, the findings of the present study support the utility of latency difference between the polarities in the diagnosis of Meniere's disease, atleast to the same degree as that of AP latency difference between the polarities.

Chapter-6

SUMMARY AND CONCLUSION

Electrocochleography (ECochG) is a technique of recording stimulus related responses or the electrical potentials of the inner ear and auditory nerve. It is employed to evaluate cochlear function in patients with Meniere's disease. The components of ECochG are eighth nerve compound action potential (AP), the cochlear microphonics (CM), and the summating potential (SP).

Various tests have been employed for the diagnosis of Endolymphatic hydrops (EH). These include Glycerol test, OAE, VEMP, CHAMP, and ECochG in addition to the conventional routine audiological evaluations. However, the reports in literature are suggestive of inaccurate and inadequate performance of these tests in the diagnosis of Meniere's disease. The reasons for this are related to relatively poorer sensitivity and specificity and occasionally the inherent problems of these tests. Hence the present study was aimed at checking the utility of latency difference between condensation and rarefaction polarities of AP and ABR in the diagnosis of Meniere's disease. The study was also aimed at comparing these two techniques with the more established SP/AP ratio.

In the present study, the conventional ABR and extratympanic ECochG were recorded from 21 ears of individuals with Meniere's disease with pure tone average less than 55 dB, 25 ears of individuals with sensorineural hearing loss other than sloping configuration and pure tone average less than 55 dB, and also 48 ears of healthy individuals. The latency of the action potential and wave I of ABR for rarefaction and condensation, and SP/AP ratio were measured

for all the group of participants. The statistics used included descriptive analysis for obtaining mean and standard deviation, Kruskal Wallis test, Mann-Whitney U test, and Kappa analysis.

The AP latency difference between rarefaction and condensation polarities in the affected ears of individuals with Meniere's disease was *significantlylarger*than all other groups of ears. The results could be explained on the basis of selective prolongation of condensation click-evoked responses due to the loading of the cochlear duct by excessive amount of endolymph (Eggermont et al., 1974; Tonndorf, 1975). Similar findings of latency difference have been reported in literature (Sass et al., 1998; Chen et al., 2004). Further, the unaffected ears of the individuals with Meniere's disease also produced *significantly larger* latency difference between the polarities compared to the other two groups (ears of individuals with sensorineural hearing loss & healthy individuals). Similar pattern of findings of affected OAE amplitude have been reported in literature in the unaffected ears of individuals with Meniere's disease (Huffelen et al., 1998). The authors discussed these findings as an indicator of progression of the disease to the unaffected ear in order to become a bilateral condition at a later point in time. The findings of the present may also be interpreted on similar lines. The ears of healthy individuals produced latency differences that were comparableto those with sensorineural hearing loss other than Meniere's disease.So the findings of the present study indicate that the latency difference of AP between the polarities could be not only useful in the identification of endolymphatic hydrops in the affected ears but also prove helpful in the early detection of onset of bilateral Meniere's in the individuals who are already suffering from the unilateral condition.

The results of the present study indicated towards a greater difference in Meniere's disease in terms of the latency difference between condensation and rarefaction click-evoked wave I of ABR. Since the wave I of ABR corresponds to the AP (Moller et al., 1983; Hall

&Antonelli, 2001), a similar prolongation of latency for condensation polarity is justified using the Eggermont et al. (1974) and Tonndorf (1975) explanation of hydropic loading on the basilar membrane. Also, the unaffected ears of the individuals with Meniere's disease revealed significantly larger latency difference for the wave I of ABR. Similar findings for OAEs have been reported (Huffelen et al., 1998) as discussed earlier for AP latency difference. This may also be implicated as an early indicator of a unilateral condition turning bilateral in the time to come.

The mean SP/AP amplitude ratio in the affected ears of individuals with Meniere's disease wassignificantly higher when compared to ears of healthy individuals, ears of individuals with sensorineural hearing loss, and also the unaffected ears of individuals with Meniere's disease.This could be related to the change in mechanics of movement of the cochlear partition that is considered important for the generation of the SP. Findings of the present are closely related to the findings of Chen et al. (2004) and on similar lines with Mori et al. (1987).

There was no significant correlation between AP latency difference and SP/AP ratio. This disagreement between the techniques may be attributed to the difference in the physiology of the AP and SP generation. Similar findings have also been reported by Ohashi et al. (2009). When both the techniques required positive results, the diagnosis could be made correctly as Meniere's disease in only 56.25% of individuals whereas a change in criterion of positive result on either of the techniques produced relevant diagnosis in nearly 85% of the individuals with already identified Meniere's disease. In addition, the SP/AP ratio also did not significantly correlate with the latency of ABR wave I. Since the AP and the ABR wave I correspond to each other, the obtained results could be expected to go on similar lines to those observed for correlation between AP latency difference and the SP/AP ratio.

The present study revealeded a strong correlation between AP latency difference and ABR wave I latency difference in the affected ears of individuals with Meniere's disease. Since wave I of ABR reflects the activity in the distal portion of the auditory nerve (Wada & Starr, 1983) and also AP corresponds to the wave I of ABR (Moller et al., 1983), a high correlation was on expected lines. This highlights the fact that ABR wave latency difference between the polarities could also prove useful in the diagnosis of Meniere's disease, a result that has never been described before.

It can be concluded that the extratympanic ECochG could be useful in the diagnosis of Meniere's disease. In addition the present study also brought to light the fact that the SP/AP ratio could be used in conjunction with the latency difference between the polarities to enhance the sensitivity in the diagnosis of endolymphatic hydrops.Another major conclusion from the study is that ABR wave I latency using rarefaction and condensation polarities can be useful in the diagnosis of Meniere's disease.

Implications

The extratympanic ECochG could be useful in the diagnosis of Meniere's disease. In addition the present study also highlighted the fact that the SP/AP ratio could be used in conjunction with the latency difference between the polarities to enhance its sensitivity in the diagnosis of endolymphatic hydrops.Further, ABR wave I latency using rarefaction and condensation polarities, could be useful in the diagnosis of Meniere's disease. Thus the outcomes of the present study could be implicated in the diagnosis of Meniere's disease. It could also enhance the chances of Meniere's disease identification by using a change in criterion and further improve the chances of early identification of a bilateral presentation of the disease condition.

Future direction

The results of the present study have left a few unanswered questions that the future researchers may take up. One of the important questions that arose as a result was to see if there would be correlation between the stage of Meniere's disease and the agreement or disagreement between the SP/AP ratio and the AP latency difference. In addition, the present study opened a new avenue of research by reporting the usefulness of ABR wave I in the diagnosis of Meniere's disease. However, the sample size of the present study would guard against its clinical use unless studies with larger sample sizes complement the preliminary findings reported in the present study.

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