Electrocochleographic Recordings from the Eardrum: Variation and Effects of Electrode Location in Normal Subjects

By

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Submitted to the graduate degree program in Hearing and Speech Department and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the Degree of Doctor of Philosophy

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Date Defended: 7/19/2012

Acceptance Page

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Electrocochleographic Recordings from the Eardrum: Variation and Effects of Electrode Location in Normal Subjects

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Date Approved: 7/25/2012

Abstract

Objectives:

The primary goals of this study are to observe the degree of variation of the tymptrode position on the TM and the marker's area size among a population of adult subjects with normal hearing, and to investigate the effects of these variations on the ECochG outcomes.

Methods:

Normative values were established for ECochG parameters. Tymptrode locations on the TM were detected by observing the gel marker in 50 TM images. 47 ECochGms were recorded for 18 normal hearing subjects. 14 subjects were tested three times and 4 subjects were tested two times. Two parameters were used to measure the location of the tymptrode on the TM: the angle and the length.

First, a mixed model was used to investigate if the tymptrode location on the TM and the marker's area size were significantly different every time the same subject was re- tested. Secondly, a mixed regression model was used to investigate if the variations of the tymptrode location on the TM affect the ECochG outcomes when all other parameters were held constant.

Results:

Results revealed that the angle of the tymptrode location on the TM was significantly different across all the measurements every time the same subject was tested. A mixed regression model results revealed no significant effect of the electrode location or the marker's area size on the SP/AP amplitude ratio. However, there was a significant effect of the angle of the marker on the SP/AP area ratio.

Most important, clinically there were no important effects of the tymptrode location variations on the ECochG outcomes.

Conclusion:

Variations of the tymptrode location on the TM had no clinically significant effects on the outcome of an ECochG exam in normally hearing subjects.

Acknowledgments

After all these years in the school and a lot of hard working with some determination and encouragement from the people around me to finish my PhD, finally I am getting close.

It would not have been possible to write this doctoral dissertation without the help and support of the kind people around me, to only some of whom it is possible to give particular mention.

First, I would like to acknowledge the faculty, staff, and students of the University of Kansas Hearing and Speech intercampus program. I specifically owe sincere thankfulness to my research advisor Dr. John Ferraro who guides me through the whole process of the dissertation writing. I am sure that this dissertation would not have been possible without his support, understanding, and encouragement I felt when working on my research. I also would like to express my gratitude to Dr Mark Chertoff for his great help and support.

I would like to acknowledge my dissertation committee Dr Francisco Diaz, Dr Gregory Ator, MD, and Dr Kostas Kokkinakis.

Special thanks and appreciations also to the staff of the Hearing and Speech Department at KUMC, especially Diane Wright, Eva Callahan and Cindy Turner.

Finally, I would like to express my sincere appreciation to my parents, my Father and my Mother. And also to my wife Diaa and my son Wesam, and my brothers and sisters.

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Chapter I

Introduction

Electrocochleography (ECochG) is a method of recording the electrical potentials of the cochlea and auditory nerve elicited by an acoustic stimulus (Pou, Hirsch et al., 1996). ECochG measurements may include: a) the cochlear microphonic (CM), which is an electrical response that mimics the acoustic waveform of the stimulus and is generated by the cochlear hair cells, b) the cochlear summating potential (SP), which is a stimulus-locked direct current potential that can be observed as a baseline shift in the CM, and also generated by cochlear hair cells, and c) the auditory nerve compound action potential (AP), which results from the simultaneous, stimulus-locked discharge of a population of spiral ganglion neurons (Margolis, Rieks et al., 1995).

ECochG has emerged as an important tool in evaluating the most peripheral events of the auditory system, especially in patients with symptoms associated with Meniere`s disease (MD) and endolymphatic hydrops (ELH). MD (also called idiopathic endolymphatic hydrops) is a disorder of the inner ear associated with episodic attacks of vertigo, tinnitus fluctuating sensorineural hearing loss, and a sensation of ear fullness (Chung, Cho, Choi, and Hung, 2004). ECochG, in combination with Auditory Brainstem Response (ABR), is also a valuable tool in intraoperative monitoring of various electrophysiological responses, to assess the functional integrity of the peripheral and brainstem portion of the auditory pathway during neurotologic procedures (Ruth and Lambert, 1989).

The morphology of ECochG recordings is highly dependent on a number of measurement parameters, such as stimulus intensity, rate, polarity and the position of the recording electrodes (Hall, 1992). With regard to this latter parameter, a variety of electrode

locations have been employed to record AP, CM and SP in both animals and humans. In animal studies, electrodes are commonly placed in the cochlea, on the round window, or directly on the auditory nerve. In humans, three recording approaches have been employed: transtympanic, tympanic and extratympanic (Ferraro & Durrant, 2006).

Transtympanic ECochG is performed by placing a needle electrode through the tympanic membrane and onto the cochlear promontory. The primary advantage of the TT approach is the close proximity of the recording electrode to the response generators, which produce components of large magnitude with little signal averaging. The major limitations for TT ECochG relate to its invasiveness. Such procedures must be performed with physician assistance (Ferraro and Durrant, 2006).

Extratympanic ECochG is performed with an electrode that is placed in contact with the ear canal wall, which is easy to perform. However, in general, response amplitudes diminish with increasing distance from the cochlea (Ferraro and Durrant, 2006).

Tympanic (TM) ECochG employs an electrode placed on the tympanic membrane. Since this site is external to the middle ear (or tympanic cavity), tympanic ECochG can also be considered an extratympanic approach. The major advantages of the TM approach are that it is noninvasive and can be performed in a non-medical setting with minimal discomfort to the patient. In addition, the response is more stable and repeatable with less signal averaging in comparison to recordings using other extratympanic approaches. A minor limitation of TM ECochG is that even with the most delicate contact between the electrode and the tympanic membrane, the tympanic membrane reacts in most cases by displaying a slight blushing spot at the point of contact. Fortunately, this reaction is temporary and causes no permanent damage to the membrane (Ferraro, 2000).

Making electrode contact with the tympanic membrane may sometimes be difficult to achieve given the variations of anatomy noted among human ear canals. If proper contact with the TM is not accomplished, less-than-ideal recordings will result. For the most part, monitoring of the electrophysiological noise floor provides ample assurance of proper electrode contact. However, additional verification via direct observation allows us to monitor the exact site of contact for each patient, and also to study the effects (if any) of electrode placement on the resultant recordings. Unfortunately, it often is difficult to see if or where the electrode is seated on the tympanic membrane via otoscopy since the tip is usually obscured by the electrode shaft in the narrow ear canal. In fact, the best way to determine these features is to observe the location of the red spot after the exam is over.

In tympanic ECochG, there have been no specific studies designed to show the relevance of electrode position on the resultant responses. Since the interpretation of an electrocochleogram often requires comparison of measurements made on separate occasions, or comparison of repeated waveforms with recognized patterns, it is important to determine if variations in electrode position on the tympanic membrane affect the response.

Although, as mentioned above, the remnant of a temporary red spot on the TM is considered to be a limitation of tympanic ECochG, the current study proposes to use this phenomenon as one of the "markers" for electrode placement. A second electrode marker is the electrode conductive gel that has been applied on the tip of the electrode. Since the tip of the electrode reset on the TM, traces of the gel generally remain there as well. For this reason, patients are instructed to rinse their ear canals with water following an examination.

Electrode location is the single most important factor affecting ECochG measurements (Norman, 2009). In transtympanic ECochG, the location of the electrode relative to the round

window is important. Since the further the electrode location is away from the round window (the generators) the smaller the amplitude of the electrocochleogram components. Dean et al. (1996) studied the effects of TT electrode position on electocohleogram. This study revealed that the electrode position in the same subject has to be repositioned in an almost identical location to obtain repeatable ECochG traces. Recording electrode positions are critical and may be part of the wide variability of ECochG recordings from different laboratories or even within the same patients on repeat exams. Roland et al. (1993) studied intrasubject variability of the ear canal electrode. Park and Ferraro (1999) studied the intrasubject variability of the TM electrode. Comparing results from both studies revealed that the variability of the tymptrode ECochG outcomes is larger than noted from ear canal recordings. Therefore, it is reasonable to assume that the variation of the place of the electrode on the tympanic membrane may play a role in outcomes variability. Based on this assumption, it may be the case that the place of the electrode on the tympanic membrane differs among, and even within subjects who undergo repeat examinations.

The primary purpose of this study is to observe the degree of variation of tympanic membrane electrode position on the TM in a population of adult subjects with normal hearing who undergo repeat ECochG testing. Once the degree of placement variability is defined, we can then investigate the effects of these variations (if any) on the resultant recordings when all other recording parameters are held constant. If the variations in electrode position on the TM are significant in the same patient in repeat exams, and/or position changes significantly affect the response, then these aspects will have to be taken into account in the interpretation of the results.

Visualization of the marker on the TM was accomplished via video otoscopy. The size and location of the marker were measured with reference to the center of the eardrum. Our study hypotheses are the following:

1- The distance between the center of the ear drum (reference point) and the center of the marker in the first test is significantly different from the distance between the center of the ear drum and the center of the marker in the second and third test within the same subject.

2- The angle of the marker from the center of the ear drum in the first test is significantly different from the angle of the marker in the second and the third test within the same subject.

3- The marker's area size in the first test is significantly different from the marker's area size in the second or third test within the same subject.

4- The SP/AP amplitude ratio and SP/AP area ratio are significantly different in the first test from the second and third test within the same subject.

Chapter II

Literature Review

The use of the electrocochleography to measure the most peripheral events of the auditory system is considered by many to be of clinical value, particularly in the diagnosis of Meniere`s disease. ECochG emerged as a clinical tool in the 1970s, even though the ability of the cochlea to generate electrical activity was realized as early as 1930, when Wever and Bray demonstrated the presence of potentials emanating from the auditory nerve of the cat in response to sound. The first report of cochlear generated potentials in humans was provided by Fromm et al in 1935. In 1947, Lempert et al demonstrated the possibility of a clinical application for Electrical Cochleogram. Summating potential (SP) was described in animals in 1950 by Davis et al, but received no attention in humans until much later. Auditory nerve Action Potential (AP) was recorded for the first time in humans in 1960 by Ruben and his colleagues while performing otologic surgery. Portman and Aran described the transtympanic technique of electrocochleography in 1971 (Deans, Hill et al. 1996).

Increased attention to all auditory evoked potentials began to occur in the early 1970s, following the discovery and clinical application of the Auditory Brainstem Response (ABR). The technical capability to record cochlear and auditory nerve potentials in humans has led to a variety of clinical applications for ECochG, the most important of which were diagnosis and monitoring of Meniere`s disease, endolymphatic hydrops, and the assessment of treatment strategies for these disorders (Ferraro, 2006).

Types of the evoked potentials

The potentials most often recorded via ECochG include the Cochlea Microphonic (CM), the Summating Potential (SP), and Action Potential (AP) of the auditory nerve.

CM is an alternating current (AC) voltage that reflects the instantaneous displacement of the basilar membrane along some distance within the cochlea. This distance is defined by the effective site and method of the recording, and the conditions of the stimulus (Ferraro & Durrant, 2006), whereas the magnitude of the CM is dependent on hair cell output and is fairly linear over a sizeable range of stimulus intensities. However, the absolute amplitude of the CM is of little value due to the dependence of the response on electrode type and placement. The CM can be recorded in humans using noninvasive procedures, but as with all neuroelectric responses, the CM decreases in amplitude as distance from the recording electrode to the generator site increases (Katz, Burkard et al., 2002).

Summating potential (SP) is stimulus related, generated by the hair cells of the organ of Corti, and a reflection of the displacement-time pattern of the cochlea partition (Ferraro, 2000). The SP tends to follow the stimulus envelope rather than its waveform. The polarities of the DC shift may be positive or negative depending on stimulus frequency, intensity and electrode recording site. When recorded with noninvasive electrodes in the ear canal or the tympanic membrane, the SP is generally characterized by a negative shift in baseline that persists for the duration of the evoking stimulus. The SP has received a good deal of attention in recent years for its application in the assessment of Meniere`s disease. The amplitude of the SP is often enlarged in patients with endolymphatic hydrops as compared to action potential (AP) (Katz, Burkard et al., 2002).

Although, the mechanism of the enlarged SP/AP ratio is not fully explained, this feature is widely accepted as a positive finding for MD. However, the sensitivity and specificity of the electrocochleography using the SP/AP area ratio in addition to the SP/AP amplitude ratio have been studied by Almomani, Ferraro, Gajewski and Ator (2009). Results indicated an improvement of the sensitivity of ECochG for diagnosing MD when SP/AP area ratio and SP/AP amplitude ratio were used together (Almomani, Ferraro, Gajewski, & Ator, 2009).

Action Potential (AP) recorded via ECochG represents the summed responses of numerous thousands of auditory fibers firing synchronously. AP, similar to the CM is an AC voltage. However, unlike either of the cochlear potentials whose waveforms reflect the displacement time pattern of the cochlear partition, the AP wave form is characterized by a series of brief negative peaks representative of the distribution of underlying neural firing. The first and larger of these peaks is referred to as N1, which is the same component as wave I of the ABR. For clinical purposes, AP magnitude and latency are the most useful features (Ferraro, 2000).

Among the first clinical reports of auditory evoked responses were descriptions of intraoperative recording of the cochlear and eight nerve activities with transtympanic (TT) electrodes located on the promontory of the cochlea. However, because of the technical difficulties associated with electrical artifact and electrode placement, ECochG failed to gain widespread acceptance (Schwaber and Hall, 1990).

The development of averaging computers and far field evoked responses led to the adoption of scalp recorded auditory brain stem response (ABR) into clinical practice; ECochG remained primarily a research tool. Recently, many studies have shown enlarged summating potential in ears with Meniere`s disease, which makes ECochG clinically valuable. Both

preoperative and intraoperative ECochG have been used to evaluate these patients and a variety of stimulus delivery and electrode configurations have been used (Schwaber and Hall, 1990).

Types of ECochG electrodes:

There are two major types of electrocochleography electrodes that were used in humans, invasive or transtympanic (TT) electrodes and noninvasive or extratympanic (ET) electrodes. The most often used invasive ECochG electrode is the TT needle. The needle is usually placed with the aid of an operating microscope, through the tympanic membrane, and on the promontory wall of the middle ear near the round window niche. Before placement, the tympanic membrane should be treated with a local anesthetic (Katz, Burkard et al., 2002). One primary advantage of this approach is that the close proximity of the recording electrode to the response generators improves signal- to- noise ratio, as a result that gives us larger components with relatively little signal averaging. However, major limitations of TT approach are that it is invasive and painful procedures even when local anesthetics are used, and it also requires the assistance of a physician in a medical setting (Ferraro, 2000).

Noninvasive or non traumatic ECochG techniques are relatively painless, thus no sedation or local anesthetic is needed. In addition, they can be placed without the assistance of a physician. There are two major types of noninvasive electrodes: extratympanic (ET) and tympanic membrane (TM) electrodes. The ET electrode was first described by Coats in 1974. It consists of an insulated silver wire with a ball tip glued to a small strip of flexible plastic, and it is placed in the ear canal. In 1986, Ferraro et al. introduced a new disposable foam-plug ear canal electrode (tiptrode). It consists of compressible foam covered by an extremely thin layer of gold foil; a plastic tube running through the center of the foam serves as a channel for stimulus delivery. These disposable foam plug electrodes are designed to compress upon insertion into the

ear canal, and expand to conform to its contour. They cannot be inserted beyond the mid portion of the ear canal. Their study showed that the foam-plug electrode recordings compared favorably with recordings obtained with a mid canal placement of the Coat. In addition, recordings were made much faster, and the electrode was easier to use. However, the amplitude of the foam-plug recordings was considerably less than the amplitude of recordings obtained with an electrode located nearer to the tympanic membrane (Ruth and Lambert, 1989).

The second noninvasive electrode is the tympanic membrane electrode or Tymptrode. It is considered the most novel approach to noninvasive ECochG. It offers a good compromise between ear canal and TT placements with respect to component magnitudes and signal averaging time and the procedures remain noninvasive and painless (Ferraro, 2000). This electrode was used for the first time in 1972 by Cullen at el. It consists of a piece of cotton which serves as the tip of the electrode. This is attached to a silver wire, and the wire is encased in flexible silastic tube. The electrode is inserted by gently sliding the tubing until the tip makes contact with the tympanic membrane (Katz, Burkard et al., 2002).

In general, comparisons between Tympanic membrane and extra tympanic recording revealed that the TM responses are less distorted, more sensitive and larger in amplitude than those measured from the ear canal (Katz, Burkard et al., 2002).

A study were conducted by Ghosh, Gupta, and Mann (2002) to evaluate and compare the results of ET and TT ECochG in clinically diagnosed cases of Meniere`s disease and controls. A stainless steel needle was used as a primary recording electrode for both methods. In the TT method, the primary electrode tip was inserted through the tympanic membrane, and was made to set on the promontory. While, in the ET method the same recording needle was inserted to the bony canal skin. The various parameters compared were summating potential latency and

amplitude, action potential latency and amplitude, and the ratio of summation to action potential (SP/AP). Results indicated a significant difference in a summation to action potential amplitude ratio between cases and controls that was obtained by both methods. Using the SP/AP amplitude ratio for diagnosing Meniere`s disease, the TT method yielded a sensitivity (true positive results) of 100% and a specificity (true negative results) of 90%, whereas, the ET method showed a sensitivity of 90% and a specificity of 80%. Based on previous outcomes, the author found that the ET ECochG was shown to be an efficacious and less invasive test as compared with the TT method (Ghosh, Gupta et al., 2002).

In another study, Ruth and Lambert (1989) compared tympanic membrane ECochG recording to TT ECochG recording in a group of patients with Meniere`s disease. In transtympanic method, the primary electrode tip was inserted through the TM, and made set on the promontory, while in TM method the electrode was made set on the TM. The ECochG recordings were examined quantitatively with regard to absolute amplitude of the summating potential and action potential. Recordings were also examined qualitatively in terms of overall waveform quality and ease of component wave identification. Results indicated that, although TM electrode recordings were smaller in magnitude, they were similar to the TT recordings in terms of overall wave form quality and identifiably of waveform components (Ruth and Lambert, 1989).

Deans et al. (1996) studied the effect of needle electrode position on the cochlear summating potential obtained in TT method. TT ECochG was performed on ten subjects with large central tympanic membrane perforation with good cochlear function. The needle electrode was accurately placed in five pre-determined positions in the middle ear. Recording were made at 4 and 8 kHz at each of the five fixed sites. Results indicated large variations both in depth and

time of the (SP) waveform. The conclusion of this study was that it is possible to obtain repeatable ECochG traces if the needle electrode is repositioned in the same subject in an almost identical position (Deans et al, 1996).

Park and Ferraro (1999) studied inter-subject test retest variability in tympanic electrocochleography. Ten normal-hearing adults were tested at six sessions. Results revealed that the variability of the SP/AP ratio in tymptrode method was larger - if compared to ear canal (tiptrode) method study by Roland et al - than the variability of the tiptrode method. It has been suspected that the electrode placement in the tymptrode method was the cause of large variations. However, amplitude was clearly larger using tymptrode, and that is mostly important in the clinic. The author concluded that the tympanic membrane ECochG is a reliable test in assessment and reassessment of normal hearing subjects (Park & Ferarro, 1999).

A preliminary study was conducted to investigate the degree of variation of the tymptrode position on the TM. Ten normal hearing subjects were tested two times. Tymptrode position on the TM for the first test was compared to the tymptrode position on the second test for each subject. Our results revealed a significant variation of the tymptrode position between the first test and the second test when all other parameters were held constant.

Despite all the studies that have been done on ECochG, there seems to be no specific research designed to investigate the effect of tymptrode site variations on ECochG outcomes variability in normal hearing subjects.

Chapter III

Methods

Testing environment:

All testing was conducted at the University of Kansas Medical Center, Kansas City, Kansas, in the Auditory Evoked Potential Laboratory of the Hearing and Speech Department.

Subjects:

Subjects comprised18 normally hearing adults; fourteen subjects were tested three times and four subjects were tested two times. All subjects had normal hearing. Thresholds were no more than 20 dB HL at frequencies .5, 1, 2, 4 and 8 KHz. All subjects tested had normal ear canal and tympanic membrane morphology with no history of otologic disorders.

Equipment and materials:

ECochG was conducted using an Interacoustics Eclipse AEP unit. The tympanic membrane ™ electrode was used in this study is the commercially available TM-EcochGtrode manufactured by Bio-Logic. It is a thin, silver chloride wire, insulated inside of a flexible silicone tube, with the end of wire encased within a conductive hydrogel molded tip, and an electrode cable lead connector at the other end as seen in Figure 1.

Figure 1: ECochGtrode by Bio-logic.

Using the TM-ECochGtrode helped us control variability that could have been associated with the physical features of the electrode such as the diameter of the tip of the electrode. Prior to use, the tip of the electrode was lightly coated with electrode gel. The other end of the electrode was connected to the preamplifier input of the AEP unit. The electrode was then ready to insert into the ear canal. Two disposable surface electrodes (secondary and ground) were attached to the contralateral mastoid or ear lobe and low forehead, respectively.

Otocam otoscopy was used to capture a colored image of the TM before and after every ECochG recording. Image J, image processing program version 1.35j, (National Institutes of Health, Bethesda, MD) was used to analyze the TM image and to calculate the area of the eardrum, the area of the marker, the angle of the marker on the TM, and the distance between the marker and the center of the TM.

Test procedures:

All subjects were required to sign the consent form that was approved by The KUMC Human subject Committee (See Appendix C). Prior to the test, all subjects were instructed that the procedures would be noninvasive and painless, and that the test would take about 30 minutes. Then the subject was placed in a supine position on a recliner. Eyeglasses and earrings were removed. Subjects were informed that two surface disposable electrodes would be attached to the scalp and ear lobes and a small gel rubber- tipped electrode would be inserted in the ear canal to rest on the eardrum. A foam earplug held the electrode in place and was also used to deliver the stimulus. If the subject reported any pain or unusual discomfort, the test was terminated. An illustration of the tymptrode in place is shown in Figure 2.

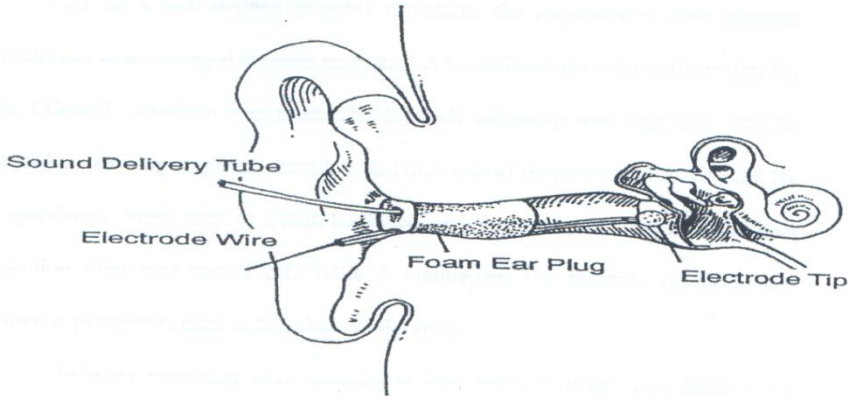

Figure 2: Illustration of the tymptrode inserted in the ear canal and resting on the eardrum (From Ferraro, 1994, Pg. 46).

Preparation of the scalp sites and ear lobes included cleaning with an alcohol swab and applying a mild abrasive (Omni Prep) to increase the surface area of electrode contact and reduce the electrode impedance. The ground and secondary surface electrodes were placed on their respective locations (low forehead and contralateral earlobe). Prior to inserting the ear canal electrode, an otoscopy was performed and a colored TM image was captured and saved to assess the patency and normalcy of the ear canal and eardrum, and to serve as a baseline picture for post test comparisons.

With the test ear facing up, the eardrum electrode was inserted into the entrance of the ear canal and gently advanced until it touched the tympanic membrane. During this process, the subject was instructed to indicate when they felt it touching the TM. Repositioning and reinsertion of the TM electrode sometimes is necessary to achieve proper contact. Every time the electrode was repositioned a new image of the TM was captured. When the electrode was properly positioned, the foam tip of the sound delivery tube was compressed and inserted alongside the electrode tubing at the entrance of the ear canal. Then, the ECochG recording commenced.

Recording Parameters:

Table I indicates the parameters that were used to record ECochG.

Electrode montage for click ECochG in the right ear was, right ear canal primary electrode, opposite ear lobe electrode or mastoid was secondary and low forehead was common site. Recording parameters were: 1000 sweeps, 10ms time window, 11.3per second stimulus repetition rate, 5 Hz low pass filter, 3 kHz high pass filter. Insert transducer ER-3 was used; the stimulus was a broad band click generated by a 100 microsecond electrical pulse presented at 95 dB nHL (0 dBnHL is the average behavioral threshold to broadband click stimulus for 10 normal subjects in our laboratory). Alternating polarity was used to reduce the appearance of the cochlear microphonic (CM) potential, and stimulus artifact. ECochG responses were recorded at least twice to insure repeatability and then averaged to produce a final waveform from which the measurements were made.

Table 1: The stimulus and recording parameters for ECochG recording to BBC stimuli.

Test	**ECochG**
Electrode Array	Tympanic membrane
Primary + Secondary – Common	Tympanic membrane. Contralateral earlobe Low forehead
Recording Parameters	
Time base Amplification Analogue band pass filter Repetition	10 msec 50,000 x 5 Hz- 3000 Hz 1000
Stimuli	
Type Duration of electrical pulse BBC Polarity Repetition rate Level	Broadband click, tone burst 100 micro second Rarefaction, condensation 11.3/ second 95 dB nHL

After ECochG was completed, the sound delivery tube, ear canal electrode and other electrodes were removed gently. A slight blushing spot on the TM at the point of contact with the tip of the electrode is a normal reaction to this procedure. This spot was used as one of the markers to locate the tymptrode position on the TM. A second marker to locate tymptrode location was the electrode conductive gel that had been applied on the tip of the electrode. Traces of both markers on the TM were recorded by video otoscopy and were documented by capturing a colored TM image immediately after removing the insert electrode. The image allowed us to maintain a photographic record of the location and extent of the marker for each subject. Then, the subject was scheduled for a repeat examination.

TM image analysis:

The TM image was saved in a computer and was inserted into the image J program. The first step in the image analysis was to define the marker of the tymptrode on the TM by comparing the post test TM image to the pre test image (baseline image). In step two, we measured the marker's area and the TM area. The marker's area for each subject was standardized by always considering it in proportion to the TM area. Also, the center of the marker's area was defined by applying a grid over the image and measuring the center point.

Next, we defined the reference point: (umbo; which is one of the anatomical land marks and the center of the TM). It was used as a reference point for all measurements of the location of the marker on the TM.

Thirdly, the ear drum was divided into four quadrants: anterior superior, posterior superior, posterior inferior and anterior inferior. This division was accomplished by drawing a vertical line along side of the manubrium, from the upper edge of the TM to the lower edge and through the reference point at the center of the TM. This vertical line divided the TM into two

halves: anterior and posterior. Then, at a 90 degree angle of the vertical line and at the level of the reference point (umbo) a horizontal line was drawn from the right edge of the TM to the left edge, passing through the reference point. This line was considered the TM diameter line, and it divided the TM into two halves; superior and inferior. We used this line also to calculate the area of the TM. Thus, both lines intersected at the reference point which was the standard reference in defining the location of the marker, this approach is shown in figure 3 below. Lastly, two measurements were used to identify the location of the marker on the TM with respect to the reference point and the TM divisions. The first measurement was accomplished by measuring the distance of the center of the marker from the reference point. It measured the variability of the location of the marker from the center of the TM. Moreover, because the depth of the otoscopy camera in the ear canal varied every time we captured a TM image, the distance of the marker from the reference point was measured in proportion to the diameter of the TM. The Second measurement was accomplished by measuring the angle of the marker location with respect to the horizontal line and the reference point. This step allowed us to identify the direction of the marker with respect to the reference point. In other words, it was used to tell us in which quadrant of the TM the electrode was located. The TM divisions are shown in Figure 3.

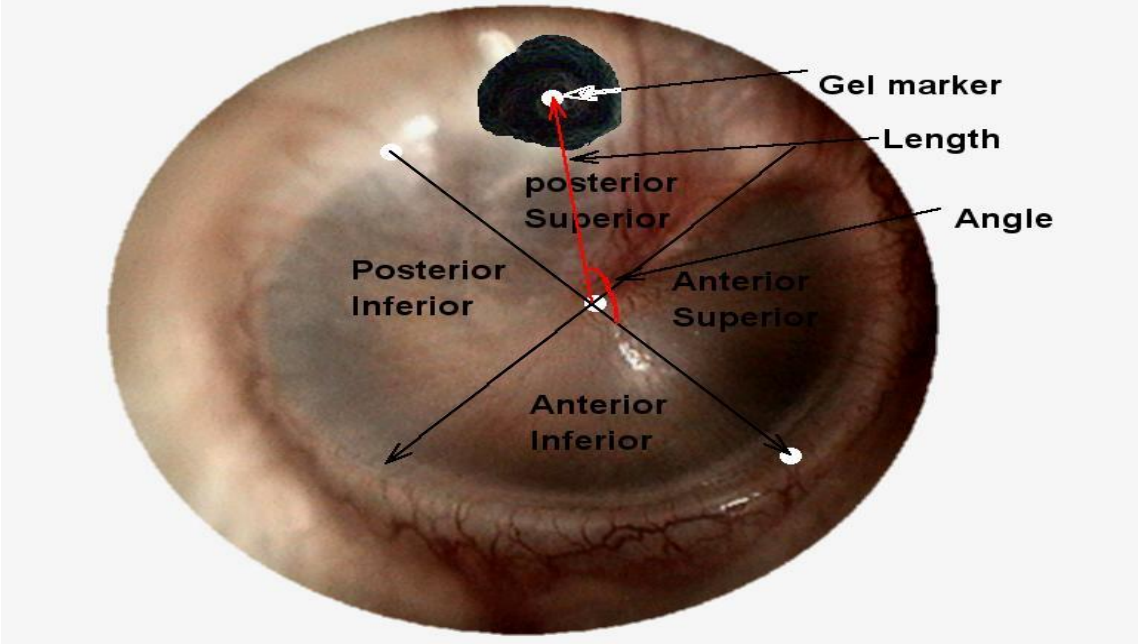

Figure 3: Right ear TM image illustrating the four quadrants of the TM and the two parameters that were used to measure the location of the electrode (angle and length).

ECochG component analysis:

SP/AP amplitude and SP/AP area ratios were measured for each subject by using the Interacoustic Eclipse EP25. As described by Ferraro and Tibbils (1999) and shown in figure 4, Sp amplitude was measured form a baseline point (i.e., SP onset) to the shoulder that represents the onset of AP1. The AP amplitude was measured from the end of SP/AP onset to the trough of N1 (AP peak). The SP area also measured as described by Ferraro and Tibbils (1999). This approach is illustrated in figure 5. A baseline point, which is prior to the start of the SP occurring at a post-stimulus onset latency of approximately 0.5 msec was defined. Once the baseline is defined, the soft ware automatically draws a baseline across the latency range of the ECochG recording to denote the next point where the waveform returns to the baseline amplitude. The area under the line was the SP area. AP area was defined as the area under the curve that started at the onset of the APN1and extended to APP1, as described by Ferraro and Tibbils (1999).

After all these markers had been defined the soft ware automatically calculated the SP/AP amplitude and area ratios.

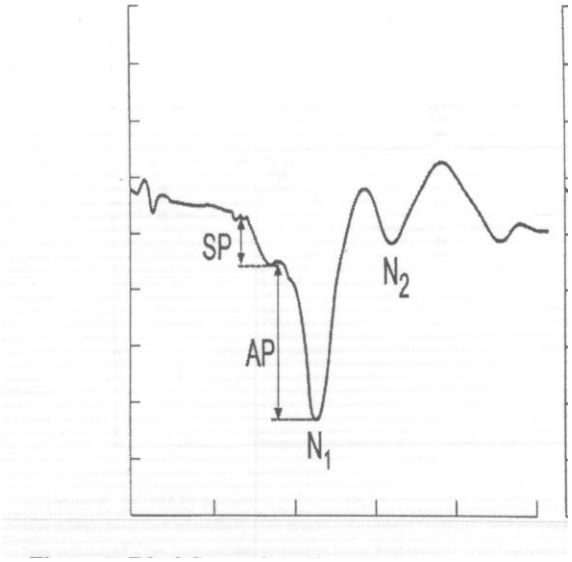

Figure 4: TM ECochG for click stimuli illustration of the AP and SP amplitude measurements. From (Ferraro 2000, P.435).

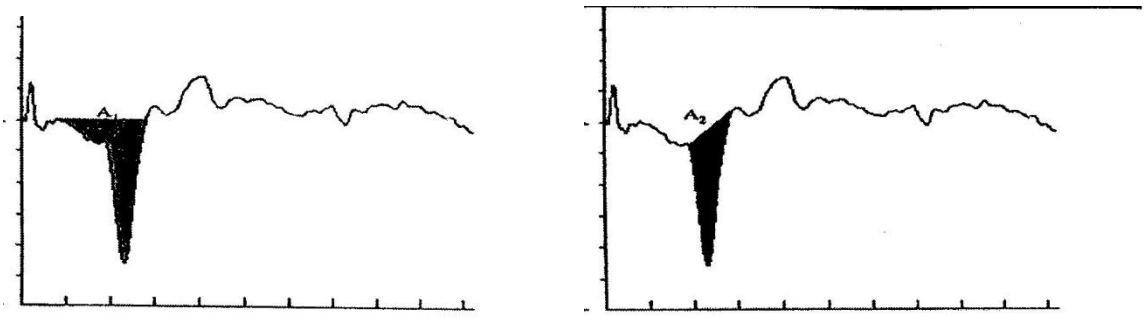

Figure 5: Measurements of the areas of the summating potentials (SP) and action potential (AP) to click stimuli to derive the SP/AP area ratio. Shaded area on the left represent SP area, while shaded area on the right represents the AP area (Ferraro and Tibbils 1999, Pg 4).

Statistical Data analysis:

The purposes of this study were first to investigate if the electrode position on the TM and the marker's area size were significantly different every time the same subject in repeat exam. Prior to the data analysis, the SP/AP amplitude ratio and the SP/AP area ratio for the Eclipse EP unit were established. Descriptive statistics were performed to determine the overall means and the standard deviations for the SP/AP amplitude and SP/AP area ratios. Then the means and the standard deviations were calculated for the first, second and third trial separately. Results were compared for consistency and reliability. The two standard deviations approach was used to determine the upper normal limit for the SP/AP area and SP/AP amplitude ratios. Also the coefficient of variation was calculated to compare between the SP/AP amplitude and SP/AP ratios variations.

The first goal of this study was to investigate if the tymptrode position on the TM and the marker's area size were significantly different every time the same subject was re-tested.

Two parameters were used to measure the location of the tymptrode on the TM: the angle and the length.

A mixed model was used to investigate if the angle of the marker was significantly different between the first, the second, and the third trials for each subject. The fixed effect of the differences across all the measurements was calculated. Fixed effect for trial one and trial two were compared to trial three to investigate if the angle of the marker was significantly different between trial one and trial three, and between trial two and trial three.

Dummy variables were created to compare between trial one and trial two to investigate if the angle was significantly different. Normal P-P plots (the observed cumulative probability

vs. the expected cumulative probability) for angle were created to assess the angle data distribution characteristic.

Same model and same procedures were used to investigate if the other two factors, the length of the marker and the marker's area size were significantly different every time the same subject was tested. Except in the marker's area size we noticed the distribution of the data did not follow the normal distribution curve. Thus, normal logarithm (LN) transformation for marker's area was performed to stabilize the variance. LN transformation was a good model for achieving good homogenous variances.

The second goal of this study was to investigate if the variation of the angle, the length, and the marker's area size had an effect on the SP/AP area and SP/AP amplitude ratios.

A mixed-effect regression model was used to test the effect of the angle, the length, and the marker's area size on the SP/AP amplitude ratio. Our regression model for SP/AP amplitude ratio and SP/AP amplitude ratio was:

$$Y= \beta0+\beta1X1+\beta2X2+\beta3X3+\varepsilon$$

Y is the SP/AP amplitude ratio. β0 is a random intercept. X1 is the angle of the marker. X2 is the length (which is distance of the marker from the reference point), and X3 is the area of the marker in proportion to the TM Area. Finally, ε is random error. It was assumed that each trial had a different variance. Covariance matrix was determined based on the correlation between different measurements within subjects. Random intercept was used to test any significant variations between subjects. P-P plots were created to examine the normality assumption of the model.

The same model was used to test the effect of the angle, length, and marker's area size on the SP/AP area ratio.

Chapter IV

Results

The overall goals of this study are to observe the variation of the tymptrode location on the TM in normal hearing subjects who undergo a repeated ECochG testing, and to investigate the effects of this variation (if any) on the resultant recording.

Different statistical analysis techniques were applied to investigate the objectives of this study. These objectives are: first, to investigate if the electrode position on the TM and the marker's area size were significantly different every time we test the same subject; second, to investigate if the electrode variations on the TM and the marker's area size variations were significantly affecting the ECochG outcomes.

Organization of this chapter is as follow:

A- Description of the data collected.

B- To investigate if there are significant differences between the electrode positions within each subject.

C- To investigate if the marker's area size varies significantly every time we test the same subject.

D- To investigate the effect of the tymptrode position and the marker's area size on ECochG outcomes (SP/AP amplitude ratio and SP/AP area ratio).

A- Description of the data collected:

Eighteen normally hearing adult subjects participated. Fourteen subjects were tested three times and four subjects were tested two times. Fifty TM images and forty seven ECochGms were collected. The mean, minimum, maximum, and the standard deviation of the SP/AP amplitude ratio and the SP/AP area ratio for first, second and third tests were calculated separately. Then, the overall SP/AP amplitude ratio and the SP/AP area ratio were calculated. Results are summarized in table2.

Table 2 : Descriptive statistics for SP/AP amplitude ratio and SP/AP area ratio.

	N	Minimum	Maximum	Mean	Std. Deviation
SpAPamp	47	.007	.437	.15260	.094681
SPAParea	47	.691	2.693	1.51626	.420462
SPAPare1	18	.980	2.693	1.51789	.430976
SPAPare2	16	.691	2.324	1.57469	.482700
SPAPare3	14	.988	2.136	1.44750	.319307
SPAPam1	18	.014	.311	.15239	.072656
SPAPam2	16	.017	.437	.16944	.123395
SPAPam3	13	.007	.273	.13215	.083793

Overall mean for the SP/AP amplitude ratio is 0.152. Overall average of standard deviation is 0.094. The upper limit for the SP/AP amplitude ratio for normal subject is equal to the overall mean plus two standard deviations (.152+.188= .34).These data suggest, for example, that a patient's SP/AP amplitude ratio maybe .05 on one visit and .34 on the next visit and still be considered within normal limits. Coefficient of variation for the SP/AP amplitude ratio was calculated by dividing the overall SD over the overall mean = .094/.152=0.60.

Overall mean for the SP/AP area ratio is 1.52. Overall standard deviation is 0.420. The upper normal limit for SP/AP area ratio was calculated by taking 2 SDs above the mean (1.52+ .84= 2.36). Coefficient of variation was calculated as 0.28.

B- Comparison of the electrode position on the TM for first, second, and third test within each subject:

Two measurements were used to identify the electrode location on the TM. First is the angle of the marker with respect to the center of the TM (reference point). Second is the length, which is the distance between the center of the marker and the center of the TM (reference point).

Angle:

Angle is defined as the measurement of the direction of the electrode location on the TM in relation to the center of the TM. The TM was divided into four equal quadrants that intersect at the center of the TM (reference point). The first quadrant is the anterior superior one that has angles starting from1degree to 90 degrees. Second is the posterior superior quadrant which has angles ranging from 91-180 degrees. The posterior inferior quadrant is the third one with a range of 181-270 degrees and finally, the fourth is the anterior inferior that ranges from 271-360 degrees. Angle variations among the three trials for all the subjects are shown in Figure 6. The mean and standard deviation for angle were calculated and the results are summarized in table 3.

Table 3: Descriptive statistic for the angle of the marker

	N	Range	Minimum	Maximum	Mean
Angle	50	331	16	347	157.16
Valid N (listwise)	50				

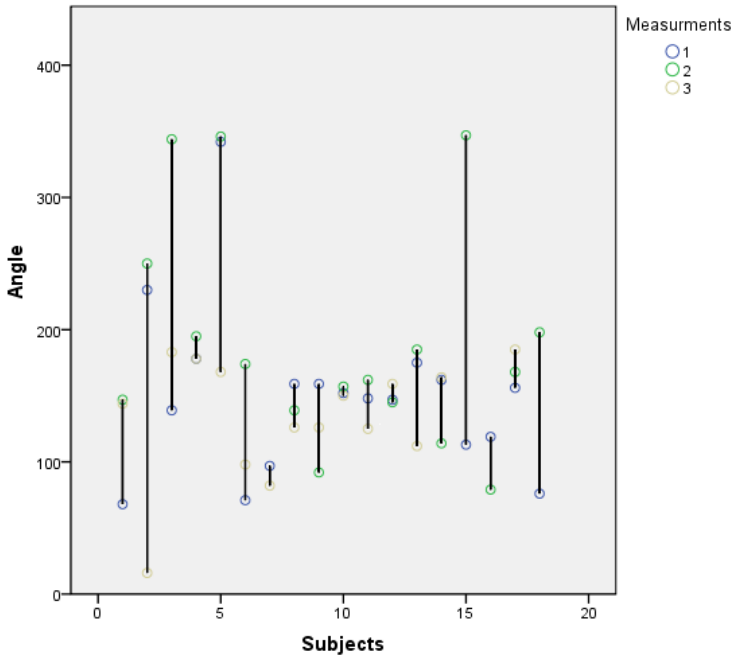

Figure 6: Variations of the angle for all the subjects among the three trials.

Our results showed that all electrode position observations on the TM were detected by the gel marker. Frequency of electrode locations on the TM were as follows: 5 observations (10%) were on the first quadrant (anterior superior), 34 observations (about 68%) were located on the second quadrants of the TM (posterior superior), 7 observations (14%) on the third quadrant (posterior inferior), and 4 observations (8%) were on the fourth quadrant (anterior inferior). Frequency of the electrode locations on the TM are shown in Figure 7.

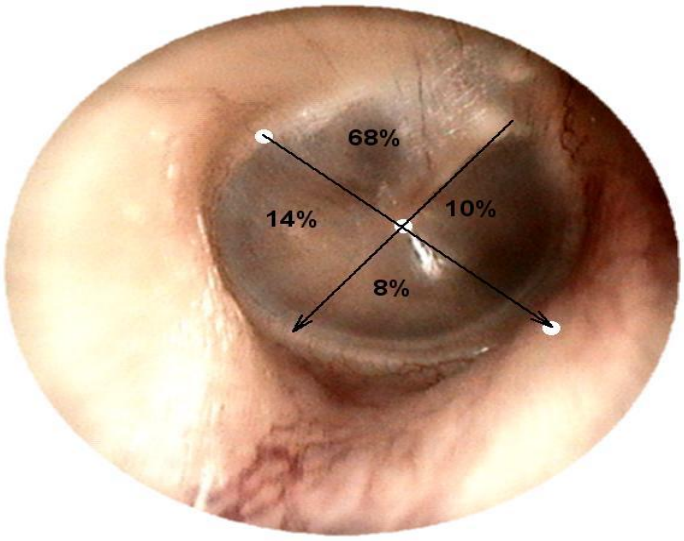

Figure 7: Right ear TM image showing the percentage of the electrode location frequency on the four quadrants of the TM.

To assess data distribution characteristics of the residuals, normal P-P (the observed cumulative probability vs. the expected cumulative probability) plots of angle for the three trials were created. Results revealed that the residuals were approximately following the normal distribution curve as seen in figure 8.

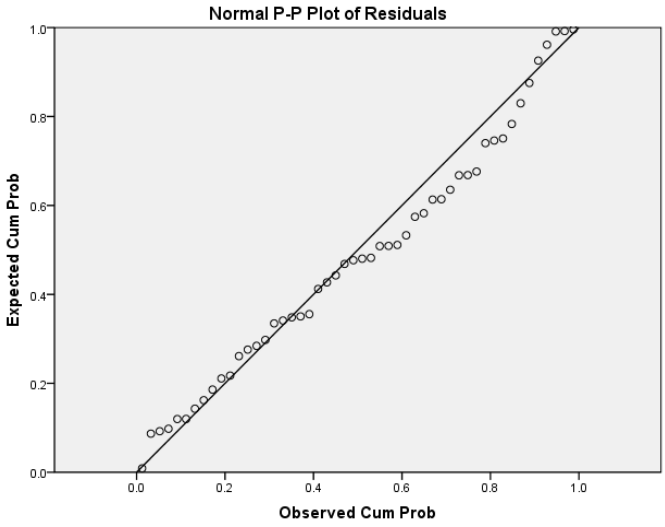

Figure 8: Display of the angle data distribution.

A mixed model was used to determine if there was a significant difference in the angle of the electrode location among the first, the second, and the third trial for each subject. Results revealed that there were significant differences across all the trials after controlling for subjects heterogeneity (p=.034), results are in table 4. Also, there was a significant difference in angle between the second and third trial (P= .013) with a mean difference of 56.2 degrees. However, no significant differences in angle between the first trial and the third trial were observed (P=.452) with a mean difference of 16 degrees, results are in table 5. Dummy variables were created to compare between trial one and trial two. Results revealed, no significant differences between them (P=.057) with a mean difference of -40 degree, as shown in table 6. Results are summarized in Figure 9.

Table 4: Comparison of the angle differences across all the trials using mixed model

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	16.575	201.477	.000
Measurements	2	31.210	3.766	.034

Table 5: Comparison of trial one and trial two of the angle to trial three within each subject using mixed model

Parameter	Estimate	Std. Error	df	T	Sig.
Intercept	133.440953	17.191165	45.345	7.762	.000
[Measurements=1]	16.059047	21.068842	31.400	.762	.452
[Measurements=2]	56.236588	21.412041	32.017	2.626	.013
[Measurements=3]	0[a]	0	.	.	.

Table 6: Comparison of trial one and trial three of the marker angle to trial two within each subject using dummy variables.

Parameter	Estimate	Std. Error	Df	t	Sig.
Intercept	189.677541	16.209604	44.275	11.702	.000
Dummy 1	-40.177541	20.275878	30.374	-1.982	.057
Dummy 3	-56.236588	21.412041	32.017	-2.626	.013

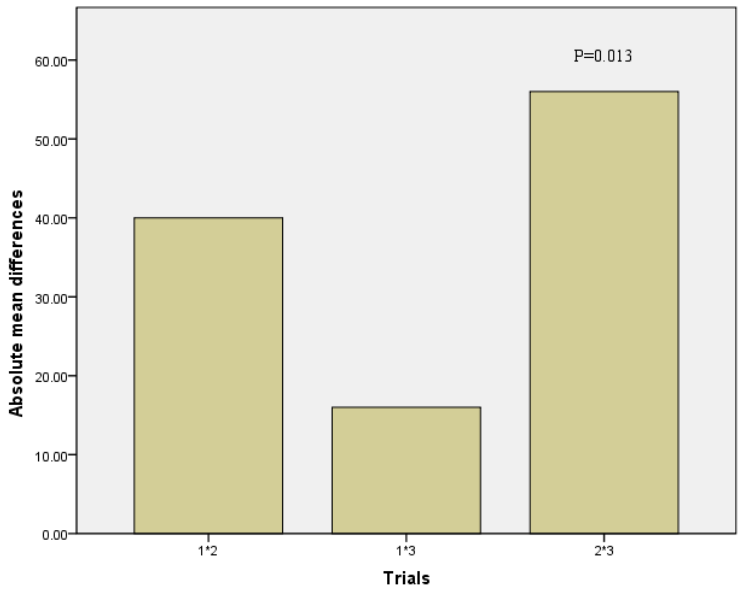

Figure 9: Comparison of the absolute value of the mean differences among the three trials. Results showed a significant difference between trial two and trial three (P=0.013).

Length:

The distance between the center of the marker and the center of the TM was the second measurement in identifying the location of the electrode on the TM. It measures how far the electrode location is from the center of TM. Because the size of the TM image varies according to the depth of the Otoscope in the ear canal, and for the purpose of controlling for this factor, the distance of the marker from the center of the TM for each image was measured in proportion

to the diameter of the TM for each image. Variations of the marker's length from the center of the TM are shown in Figure 10. Descriptive statistics were performed. Results are summarized in table 7.

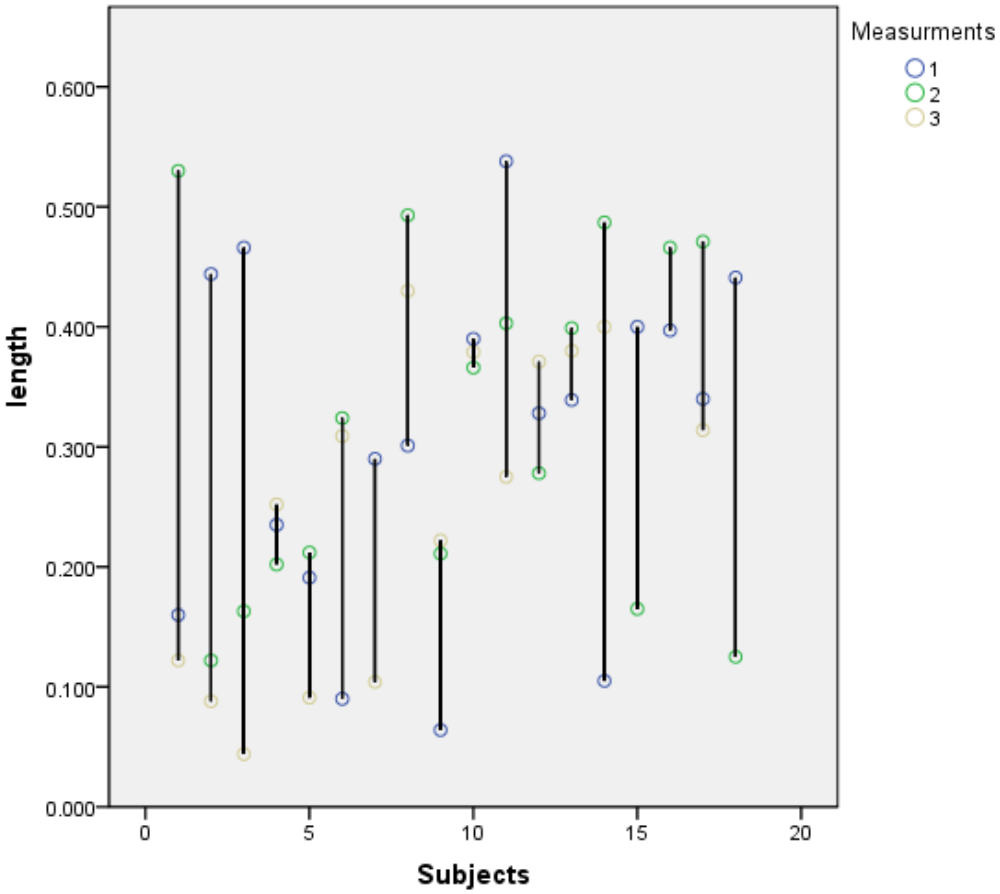

Figure 10: Variations of the marker's length in pixels from the center of the TM across all subjects for the three trials.

Table 7: Descriptive statistic for the marker's length from the center of the TM.

	N	Minimum	Maximum	Mean	Std. Deviation
length	50	.044	.538	.29434	.138410
Valid N (listwise)	50				

To assess data distribution characteristics of the residuals, normal P-P (the observed cumulative probability vs. the expected cumulative probability) for the length, residuals were normally distributed as seen in figure 11.

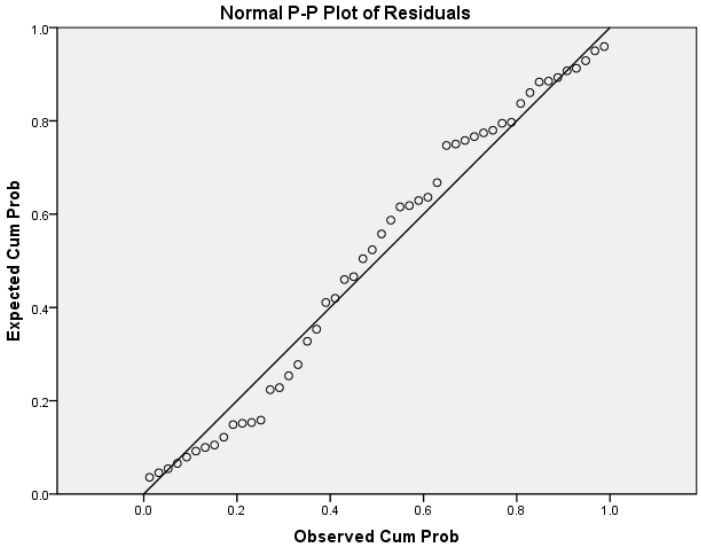

Figure 11: Display of length data distribution.

A mixed model was used to investigate if the distance between the center of the TM and the center of the marker (length) was significantly different among the first, the second and the third trials. Results revealed no significant differences across subjects after controlling for subjects heterogeneity (p= .359). As seen in table 8. Comparisons between trial one and three, and trial two and three also were conducted. Results revealed no significant differences between trial one and trial three (p=.260) with a mean difference of (.054 pixel), no significant differences between trial two and trial three (p=.179) with a mean difference of (.0657 pixel) as seen in table 9.

Dummy variables were created to compare between trial one and trial two. Results revealed no significant difference (p=.801) with a mean difference of (-.0657 pixel) as seen in table 10.

Table 8: Comparison of the length across the three trials using mixed model.

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	17.408	204.890	.000
Measurements	2	32.648	1.056	.359

Table 9: Comparing trial one and trial two of the length to trial three using mixed model

Parameter	Estimate	Std. Error	df	t	Sig.
Intercept	.252419	.035698	46.930	7.071	.000
[Measurement=1]	.054192	.047314	32.896	1.145	.260
[Measurement=2]	.065798	.047979	33.607	1.371	.179
[Measurement=3]	0[a]	0	.	.	.

Table 10: Comparison of trial one and trial three of the length to trial two within each subject using dummy variable.

Parameter	Estimate	Std. Error	df	t	Sig.
Intercept	.318218	.033540	46.869	9.488	.000
Dummy1	-.011606	.045708	31.639	-.254	.801
Dummy3	-.065798	.047979	33.607	-1.371	.179

C- To investigate if the marker's area size is significantly varying every time we test the same subject:

Gel markers were detected in all subjects to determine the location of the electrode on the TM. The marker's area size was measured in proportion to the entire TM area to investigate if the electrode marker' area was significantly different every time we tested the same subject. Because the otoscopy prop's depth in the ear canal varied every time we captured a TM image,

the marker's area size was measured in proportion to the TM area for each trial. Variations of the marker's area size for the three trials across all the subjects are shown in Figure 12.

To assess data distribution characteristics of the residuals, a normal P-P (the observed cumulative probability vs. the expected cumulative probability) plot of the marker area was created. P-P plot indicated that the residuals were significantly skewed as shown in Figure 13. Normal logarithm (LN) transformation for marker's area was performed to stabilize the variance. As seen in Figure 14, the LN transformation was a good model for achieving good homogenous variances.

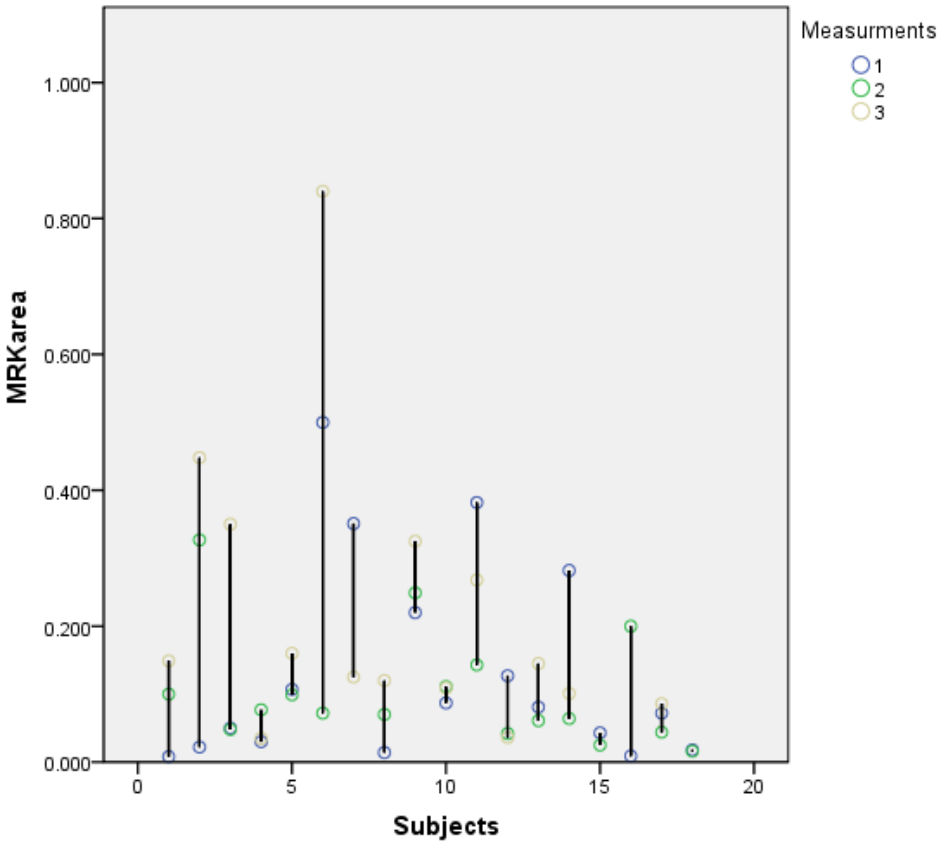

Figure 12: Variations of the marker's area size across all the subjects for the three trials.

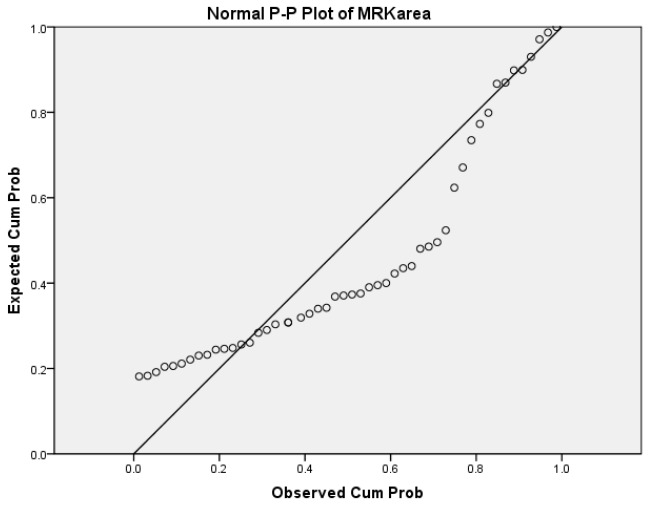

Figure 13: Display of the marker's area size distribution.

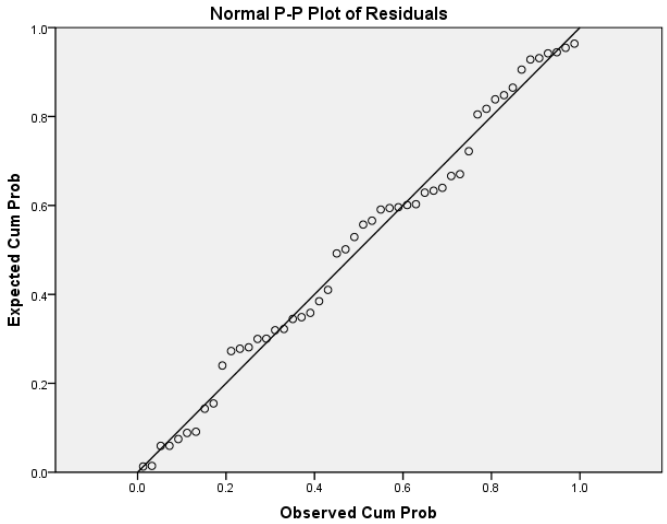

Figure 14: Display of the marker's area size distribution after normal logarithm transformation.

A mixed model was used to investigate if the size of the marker's area was significantly varying every time we tested the same subject. Overall, results revealed no significant differences among the three trails (P=.060), results are in table 11, however, there was a significant difference between trial one and three (P=.023) with a mean difference of 60% lower than the marker's area size for trial three. However no significant differences between trial two

and trial three were observed (P=.072) as seen in table12. Dummy variables were created to compare between trial one and trial two. Results revealed no significant differences (p=.608). Results are summarized in Table 13.

Table 11: Comparison of the marker's area size differences across the three trials.

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	15.741	201.009	.000
Measurements	2	30.426	3.092	.060

Table 12: Comparing trial one and trial two of the marker's area size to trial three using mixed model.

Parameter	Estimate	Std. Error	df	t	Sig.
Intercept	-1.923906	.263577	45.459	-7.299	.000
[Measurements=1]	-.779296	.325420	30.627	-2.395	.023
[Measurements=2]	-.616808	.330663	31.271	-1.865	.072
[Measurements=3]	0[a]	0	.	.	.

Table 13: Comparing trial one and trial three of the marker's area size to trial two using dummy variables

Parameter	Estimate	Std. Error	df	t	Sig.
Intercept	-2.540714	.248413	44.437	-10.228	.000
Dummy1	-.162489	.313264	29.553	-.519	.608
Dummy3	.616808	.330663	31.271	1.865	.072

D- To investigate the effect of the TM electrode location (length, and angle) and the marker's area size on the SP/AP area ratio and SP/AP amplitude ratio.

1- To investigate the effect of the marker's angle, length and the marker's area size on the SP/AP area ratio.

Two measurements were used to identify the location of the electrode on the TM, The angle of the marker in respect to the center of the TM, and the distance from the marker center to the TM center (the length). A mixed-effect regression model was used to investigate the effects

of these two measurements (angle, length) and the effect of the marker's area size on the SP/AP area ratio. Our regression model for the SP/AP area ratio is:

$$Y= \beta0+\beta1X1+\beta2X2+\beta3X3+\varepsilon$$

Y is the SP/AP area ratio. β0 is a random intercept. X1 is the angle of the marker. X2 is the length, the marker's area size in proportion to the TM Area. Finally, ε is a random error. It was assumed that each trial had a different error variance, and that there were no significant correlations between different measurements within subjects for the SP/AP area ratio. Thus, the diagonal matrix for the within subject errors was used in this model. There was no evidence of or unexplained significant variation between subjects, so it was unnecessary to use random intercept. The fixed effects model revealed no significant effect of the length or the marker's area size on the SP/AP area ratio. However, there was a significant effect of the angle on the SP/AP area ratio (P = .031) and with a regression coefficient estimate of (-.002144 μv.ms /degree). This means that in every one degree angle increase, SP/AP area ratio decreased by 0.002144 μv.ms. Results are shown in table 14.

Table 14: Estimates of fixed effect of the angle the length and the marker' area size on the SP/AP area ratio.

Parameter	Estimate	Std. Error	df	t	Sig.
Intercept	1.627363	.224417	34.817	7.252	.000
Angle	-.002144	.000952	35.285	-2.253	.031
length	.354268	.445248	37.156	.796	.431
lnmarker	-.043425	.062700	32.691	-.693	.493

To assess data distribution characteristics of the residuals, normal P-P (the observed cumulative probability vs. the expected cumulative probability) plots of the model were created. As we can see in figure 15, residuals are approximately following the normal distribution curve.

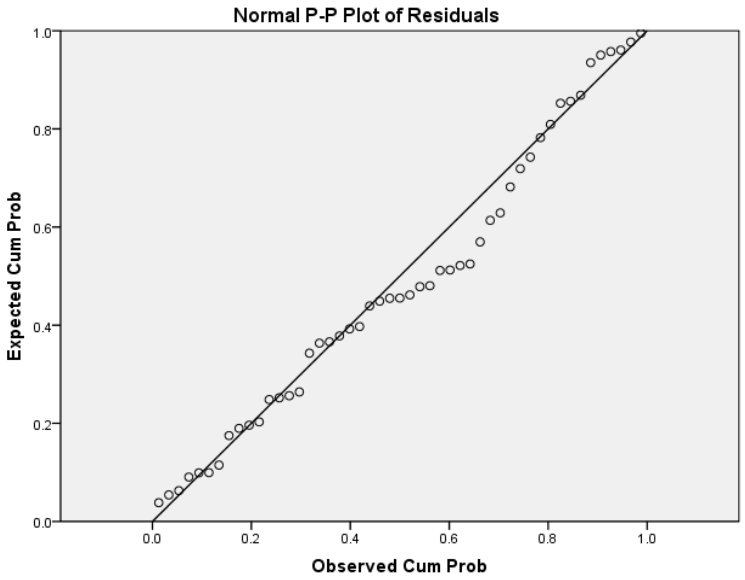

Figure 15: Display of the data distribution for the mixed regression model of the SP/AP area ratio and the angle.

An interclass correlation (ICC) for the SP/AP area ratio was performed to test the reliability among the three test trials. ICC= intercept variance/ total variance = .009654/.177484= .054. Results revealed weak correlation among the three trials. Scatter plots were created among the three trials to assess the correlations. Results showed weak correlations as seen in Figures 25, 26, and 27 in Appendix B.

2- To investigate the effect of angle, length, and marker's area size on the SP/AP amplitude ratio.

A mixed-effect regression model was used to investigate the effect of the TM electrode position and the marker's area size on the SP/AP amplitude ratio. Our regression model is $Y= \beta0+\beta1X1+\beta2X2+ \beta3X3+\varepsilon$. Y is the SP/AP amplitude ratio. β0 is a random intercept. X1 is the angle of the marker. X2 is the length, and X3 is the marker's area size in proportion to the total TM Area. Finally, ε is random error. It was assumed that each trial had the same error variance, and no significant correlation between the different measurements for the SP/AP area

ratio. Thus, a scale identity matrix was used in this model. Results revealed no significant effect of the angle or the length or the marker's area size on the SP/AP amplitude ratio. Results are summarized in table 15.

Table 15: Estimates of fixed effects for the angle, the length and the marker's area size on SP/AP amplitude area.

Parameter	Estimate	Std. Error	df	t	Sig.
Angle	-.000191	.000208	40.683	-.917	.364
lnmarker	.004898	.013415	39.339	.365	.717
length	.067919	.099969	38.761	.679	.501

To assess data distribution characteristics of the residuals, normal P-P (the observed cumulative probability vs. the expected cumulative probability) plots of the model were created. As shown in figure 16, the residuals are approximately following the normal distribution curve.

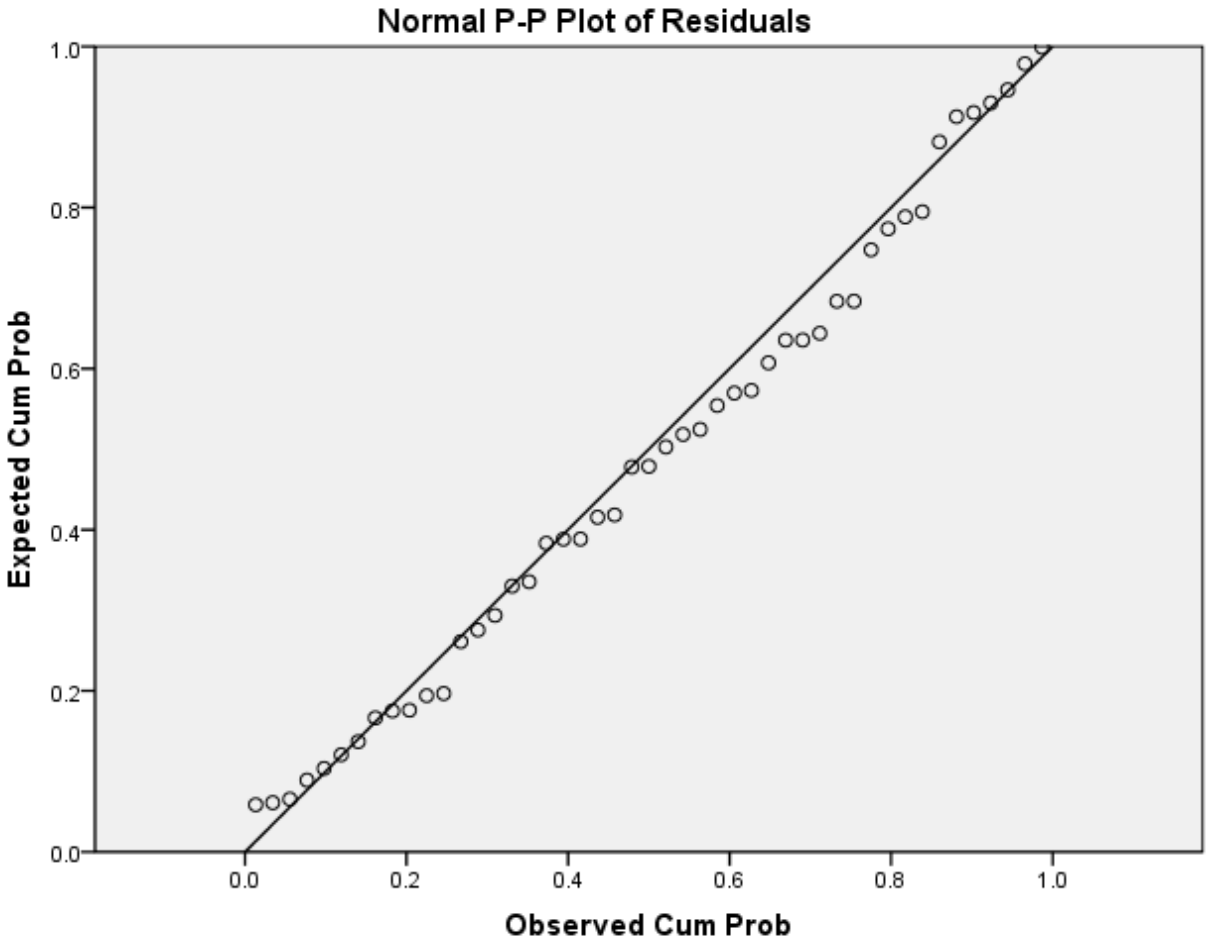

Figure 16: Display of the data distribution for the mixed regression model of the SP/AP amplitude ratio with angle.

An interclass correlation for the SP/AP amplitude ratio was performed to test the reliability among the three trials. Interclass correlation = intercept variance/ total variance. ICC= .001501/.008755=.1714. Results revealed weak correlations among the three trials. Scatter plots among the three trials were created to assess the correlation. Results revealed weak correlations among the three trials as can be seen in Figures 28, 29 and 30 in Appendix B.

Chapter V

Discussion

The primary objectives of this study were: first, to investigate if the tymptrode location on the TM was significantly different every time we re-tested the same subject and second, to investigate if the variations of the tymptrode location and the marker's area size have a significant effect on the ECochG outcomes.

The organization of this chapter discusses the results in the following order:

A- Description of the Data collected.

B- Variations of Tymptrode location on the TM.

C- Variations of the marker's area size.

D- The effects of the tymptrode location and the marker's area size on the SP/AP amplitude ratio.

E- The effects of the tymptrode location and the marker's area size on the SP/AP area ratio.

A- Description of the data collected.

The first step in this study was to establish normal values for the SP/AP area ratio, and the SP/AP amplitude ratio for the Eclipse AEP unit, since this unit is new and these values are yet to be standardized in the literature. Only a few studies have reported normal values for the SP/AP amplitude ratio. Ferraro and Tibbils (1999) reported a mean of 0.21μV with a 0.10 standard deviation (SD), and an upper normal limit of 0.41μV (mean +2SD) for the SP/AP amplitude ratio. Park and Ferraro (1999) used the 95 percentile of the cumulative distribution curve to determine the upper normal limit; they reported a 0.43μV as an upper normal limit.

Almomani and Ferraro (2009) reported a 0.35µV as an upper normal limit using the mean plus 1SD. In our study, the SP/AP amplitude ratio upper normal limit was 0.34 µV using the mean plus 2SDs. Cumulative distribution curve was created for the SP/AP amplitude ratio, as Figure 17 shows that ninety five percent (95%) of the sample population of our data had 0.33 µV or below.

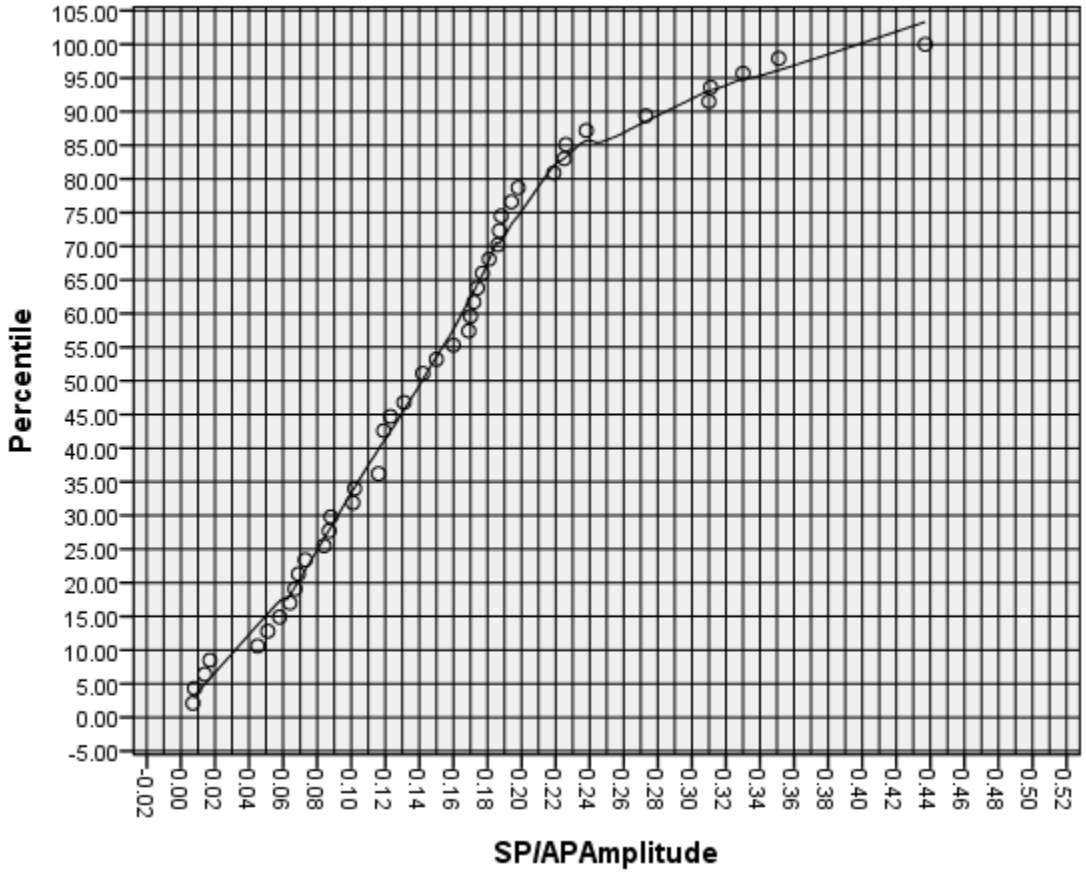

Figure 17: Cumulative distribution curve of the SP/AP amplitude ratios recorded from 18 normal subjects. Ninety-five percent of the sample population had normal SP/AP amplitude ratios of .33 or below.

In comparison, even fewer studies have reported normal values for the SP/AP area ratio. Ferraro and Tibbils (1999) reported 1.37 µVmsec as an upper normal limit for SP/AP area ratio. Almomani et al, (2009) reported 0.87 (mean, 0.53; 1SD of 0.14) as the upper normal limit for SP/AP area ratio. Devaiah et al, (2003) reported 1.94 as an upper normal limit (mean, 1.34;

SD, 0.3). In our study, our upper normal limit was 2.34 (mean, 1.5; SD 0.42). 2SDs was used as our determination for the upper limit for normal. Cumulative distribution curve of SP/AP area ratio was created. As shown in figure 18, our ninety five percent was 2.3.

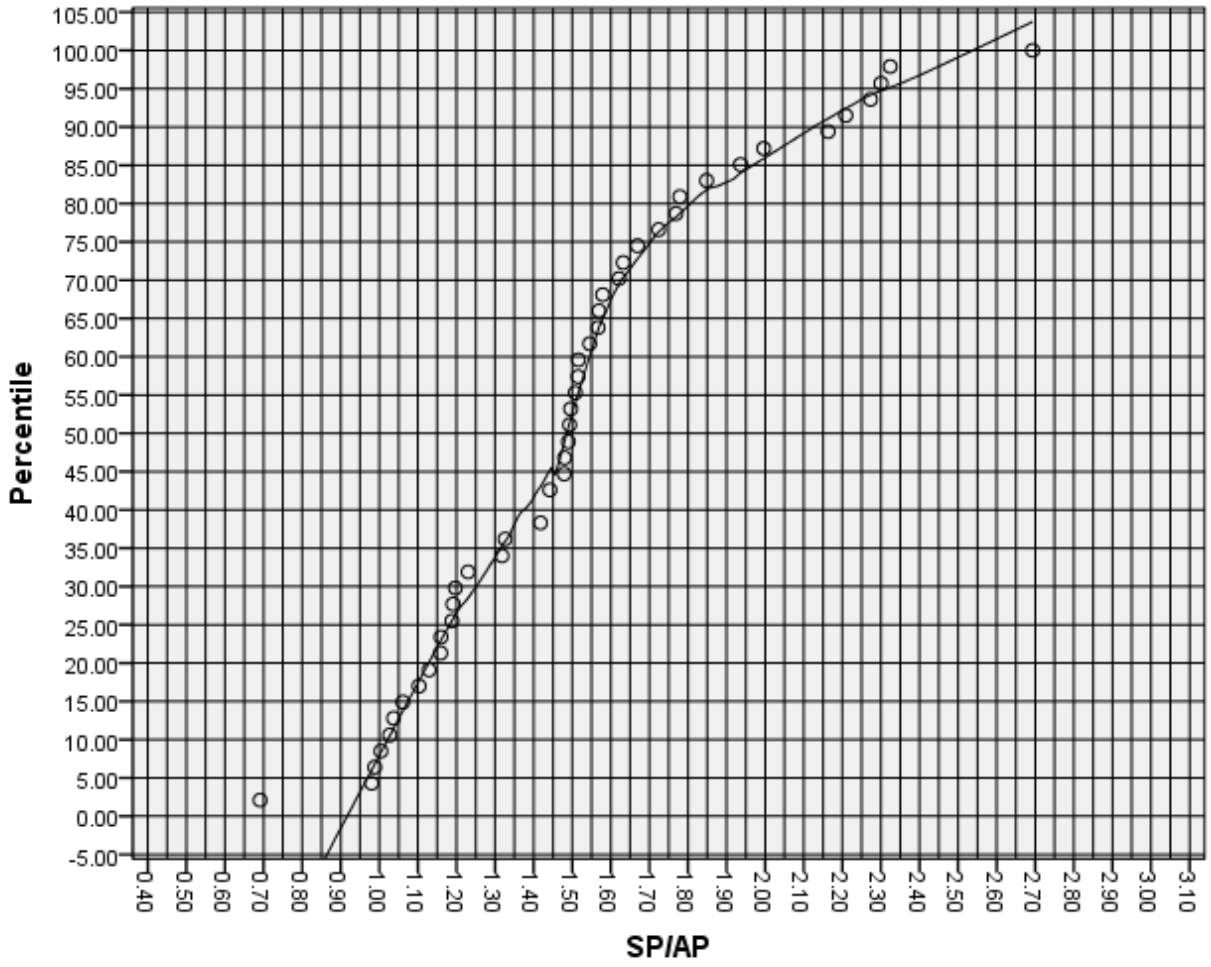

Figure 18: Cumulative distribution curve of the SP/AP area ratios recorded from 47 data points. Ninety-five percent of the sample population had normal SP/AP area ratio of 2.30or below.

Besides instrumentation and examiner's expertise factors, the difference between the SP/AP amplitude ratio in our study versus the other studies is due to different approaches that have been used to calculate the upper normal limit. Some have used the mean plus 2SDs (Ferraro and Tibbils, 1999 and Ferraro and Devaiah, 2003), while others used the mean plus 1SD (Almomani et al, 2009), Park and Ferraro (1999) used the 95^{th} percentile.

In addition to what is mentioned above, differences between the SP/AP area ratio in our study versus other's is due to the different manner in measuring this value. In our study, the Eclipse unit defined the SP area as the total area of the SP-AP complex, which then was divided by the AP area to derive the SP/AP area ratio. Almomani et al (2009) defined the SP area by subtracting the AP area from the total area of the SP-AP complex, and then divided it by the AP area to derive the SP/AP area ratio.

Another factor that might affect the variability in this study is the trailing edge of the SP- AP complex. In normal subjects the trailing edge of the SP-AP complex usually returns to the baseline. Our clinical protocol defined the SP area as the area under the line that connects between a baseline points prior the onset of the SP, and a second point where the SP-AP complex returns to the baseline (P2) and it usually does not include the N2 area. But in our study we noticed that the trailing edge of the SP-AP complex in 28 out of 50 observations did not go back to the baseline, and that was not associated with a specific location of the electrode on the TM. As a result N2 area was added to the SP area, and that made the SP area larger. Our standard deviation for the SP/AP was 0.42 while Ferraro and Tibbils (1999), and Almomani et al (2009) reported 0 .11 and 0.13 SD, respectively. In addition, our SP/AP area mean was larger than reported in the other studies for the same reason. These findings made the variability and the upper normal limit for our study larger in comparison to the other studies.

The large variability associated with the SP/AP area ratio had an impact on the coefficient of variation. Our results showed that the SP/AP area ratio varies about 28% of the mean, while the SP/AP amplitude ratio variation is 60% of the mean.

B - Variations of the tymptrode location on the TM.

TM ECochG is an effective non-invasive approach in the diagnosis of MD. It offers a good compromise between the ear canal and the transtympanic approach with respect to the component magnitudes and signal averaging because of the noninvasiveness of the approach and the close proximity of the electrode to the response generators.

Unfortunately, with the TM approach it is often difficult to see where the electrode is seated on the TM via Otoscopy, since the tip is usually obscured by the electrode shaft in the narrow ear canal. Thus, in every TM ECochG the electrode is set blindly on the TM. The best way to identify the location of the electrode on the TM is by observing the markers after the exam is over. Two markers were observed to locate the electrode position on the TM. First, is the red spot marker, which is a normal reaction of the TM at the point of contact with the electrode. It normally disappears after a short period of time. This marker was detected in our preliminary study, but in this study none of the electrode locations were defined by this marker.

The second marker was the conductive gel that we applied on the tip of the electrode. All the electrode positions in this study were detected by the gel marker. In contrast to the red spot marker, the gel marker is more accurate in identifying the location of the electrode because its area size is smaller than the red spot, and it more closely resembles the actual size of the tip of the electrode. However, sometimes it is hard to detect the gel spot on the TM because it has no color and in some cases the ear canal hairs obscure and limit the amount of gel reaching the TM. Moreover, it was initially noticed that the gel could have remained on the TM for a

longer period of time. For example, gel marker was detected in one case a week after testing. To counter this, subjects were instructed to flush their ears after examination.

Two parameters were used to measure the marker location on the TM. First was the angle, which represents the quadrants of the TM. It tells us in which quadrant of the TM the marker is located. In this study about 68% (34 observations) of the time the electrode was placed in the posterior- superior quadrant of the TM. These results agree with our finding in the preliminary study, and indicate there is a 68% chance that the electrode will sit on the posterior-superior quadrant of the TM every time we insert it. We observed that the anatomical feature of the ear canal plays a role in the electrode location on the TM when we tested the same subject. The ear canal has a bend where the outer cartilaginous part joins the bony inner part of the canal. That bend runs somehow backwards, and in normal ears the bend varies between sharply bending backward and slightly bending backward. In some cases, when we inserted the electrode, the morphology of the ear canal tended to lead the tip of the electrode to the posterior part of the TM.

A mixed model was used to investigate if the marker's angle was significantly different among the three trials. Results revealed a significant difference between trial two and trial three, but no significant differences in the marker's angle between trial one and three or trial one and trial two. There was a significant variation of the angle across all the subjects. This finding is consistent with our pilot data, and this variation was expected since the electrode was placed on the ear drum blindly. Although our results showed that 68% of the time the electrode was placed on the posterior-superior quadrant, the angle was different every time.

The second parameter that was used to measure the location of the electrode was the distance between the center of the marker and the center of the TM (i.e. length). A mixed

model was used to investigate if the electrode location on the TM significantly varied in respect to the center of the TM (umbo) among the three trials for each subject. Results revealed no significant differences between the three trials or across all the trials. That means that there were no significant variations for the electrode in the area between the center of the TM (umbo) and the edge of the TM (radius of the TM). Because this area is smaller compared to the angle's area less variability in length is expected.

C – Variations of the marker's area size.

A mixed model was used to investigate if the marker's area size was significantly different between the three trials for each subject. Results revealed significant differences between trial one and trial three, but no significant differences were noticed between trial one and trial two, or trial two and trial three. Overall, there were no significant differences across all the subjects in the marker's area size. Usually when we applied the conductive gel to the tip of the electrode we randomly dipped the electrode into the gel, so the amount of the gel may have varied every time, but it closely resembled the actual size of the tip of the electrode.

D – Effect of the angle of the marker and the Marker's area size on SP/AP amplitude ratio.

A mixed-effect regression model was used to investigate the effects of the angle, the length, and the marker's area size on the SP/AP amplitude ratio. Our regression model is $Y=\beta0+\beta1X1+\beta2X2+\beta3X3+\varepsilon$, where Y is the SP/AP amplitude ratio, β0 is a random intercept, X1 is the angle, X2 is the length,X3 is the marker's area size, and ε is a random error. Our results revealed no significant affect of the angle, the length, and the marker's area size on the SP/AP amplitude ratio.

The effect of the electrode position on the human SP obtained by TT ECochG was studied by Dean et al. in1995. A needle electrode was placed in five predetermined positions

from a reference point in the middle ear. Tone pip stimuli at 4 KHz and 8 KHz were used. Results revealed a large variation of SP amplitudes at different locations within the same subjects. One subject showed a 100% increase from anterior to inferior position at 4 KHz. Another subject showed a 500% increase from anterior to inferior position. Also, there was no tendency for a specific position to be associated consistently with large or small values. In addition, there was a significant difference between subjects at 4 KHz and 8 KHz. Re-setting the electrode in a nearly identical position gave good reproducibility.

In this study, variations of the angle of the electrode position on the TM were significantly different every time we tested the same subject. Those variations had no significant effect on the SP/AP amplitude ratio, with a smaller variation to the SP amplitude as exemplified with subject number 3 in our study. In the first trial, the marker's angle was 139 degrees, SP amplitude was.382 and the SP/AP amplitude ratio was 0.169. In the second trial the angle was 344 degrees, the SP amplitude was 0.169 and the SP/AP amplitude ratio was 0.116. While in the third trial the angle was 183 degree, SP amplitude was 0.345μv and the SP/AP amplitude ratio was .225μv. The large variations in the SP amplitude in Dean's study were due to two factors. First, transtympanic SP can be described as a localized near field effect response, and is more likely to be affected by the location of the electrode especially when it is generated in response to high frequency stimuli which activate the basilar membrane in basal turn of the cochlea. Any electrode deviations from the reference point will cause large variability. The second factor is the size of the electrode tip. Since a needle electrode was used in the TT approach, the tip of the needle is usually very thin in comparison to the tymptrode or an ear canal electrode. Thus, it is difficult to place the electrode in the middle ear on the exact location every time the same subject is tested, especially if the eardrum is intact. The close proximity of the TT approach to the

response generators improves signal to noise ratio, resulting in larger components with little signal averaging. However, a major limitation of the approach beside its invasiveness is the large variability that is associated with the electrode position in the middle ear if the needle electrode does not re-position at the same location. By comparison, the TM ECochG approach is a more a far field one, where slight variations in electrode placement are not expected to produce significant effects on the response. The results of this study supported this contention, in that variations of the electrode location on the TM had no significant effect on the SP/AP amplitude ratio. This finding represents an advantage of the TM approach over the TT approach.

The variability of the ear canal electrodes was studied by Roland et al (1993), while Park and Ferraro (1999) studied the variability of the TM electrode. Variations in the SP/AP ratio were larger for TM ECochG in comparison to ear canal recordings, again reflecting a near-field-far field effect. In addition, the ear canal electrode is easy to place in the same position every time, and covers more surface area than a tymptrode. These factors also contribute to less variable recordings. Although larger variability is associated with tymptrode position on the TM, we consider the advantage of larger components to be greater to the clinician than the smaller variability associated with the ear canal approach, especially when we know that tymptrode variations on the TM have no significant effect on the SP/AP amplitude ratio, as our results showed.

Clinically our results showed no important effect of the angle of the marker on the SP/AP amplitude ratio. Our upper normal limit was determined earlier in the study. It was .34μV. only two observations were above the normal limit subject 18 second trial and subject 17 second trial. Subject 18 in the first trial, the angle was 198, Figure 19 shows us the TM image before ECochG recording, and Figure 20 shows the TM after ECochG recording where the gel

marker was on the posterior inferior quadrant of the TM. Also Figure 21 shows ECochG response and the measurements for SP/AP amplitude ratios, it was 0.194µV. While the second trial as shown in Figure 22, the gel marker is located on the anterior superior quadrant, the angle was 76 degrees and in Figure 23, SP/AP amplitude ratio was 0.437µV. In comparison to subject 6 trial one, where the angle was 71 degrees and the SP/AP amplitude ratio was 0.238, this variation seems to not be associated only with the location of the tymptrode.

Figure 19: Left ear TM image for subject 18 prior to ECochG recording in the first trial.

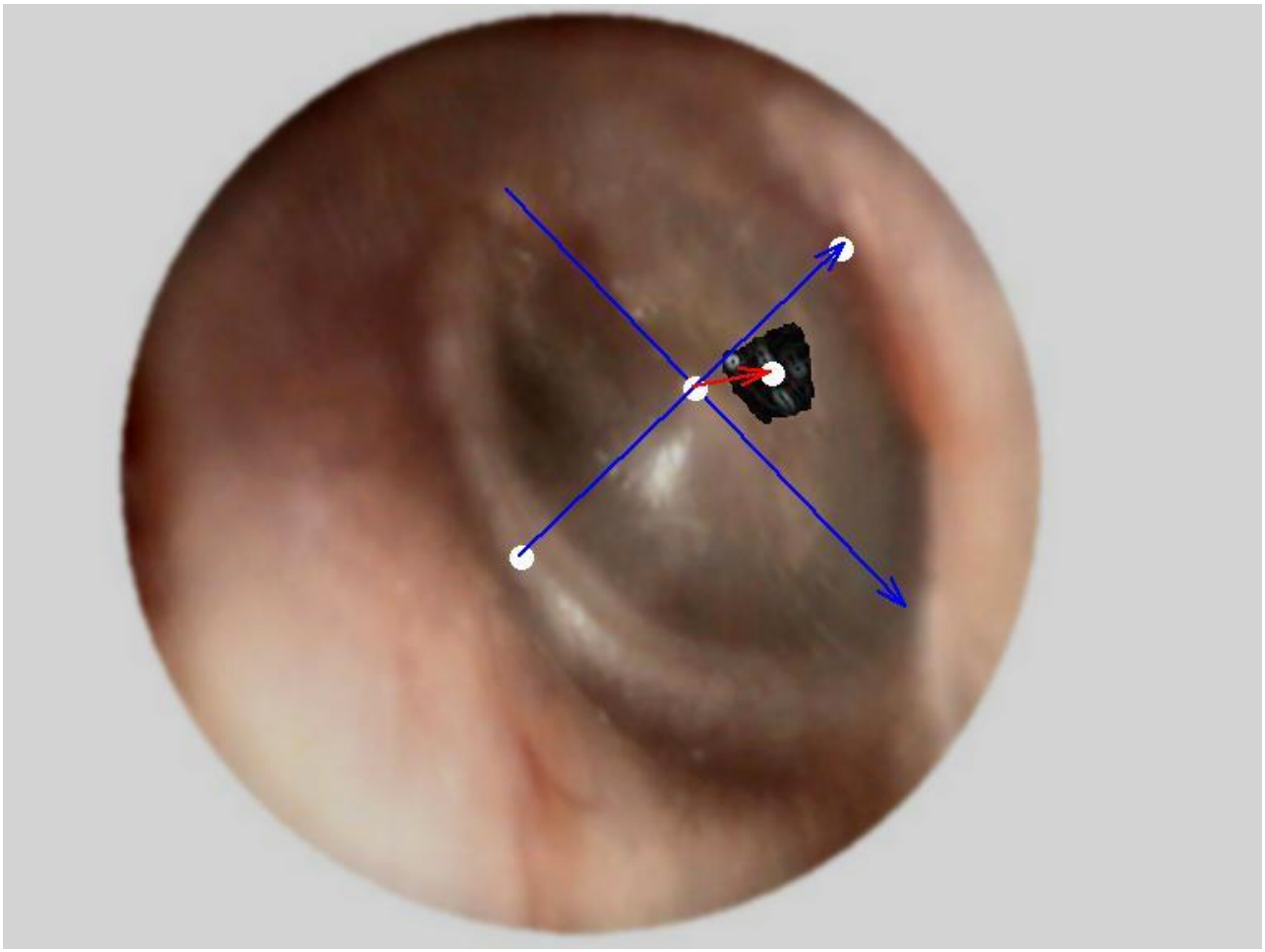

Figure 20: Left ear TM image for subject 18 after ECochG recording in the first trial. Tymptrode was sitting on the posterior inferior quadrant of the TM.

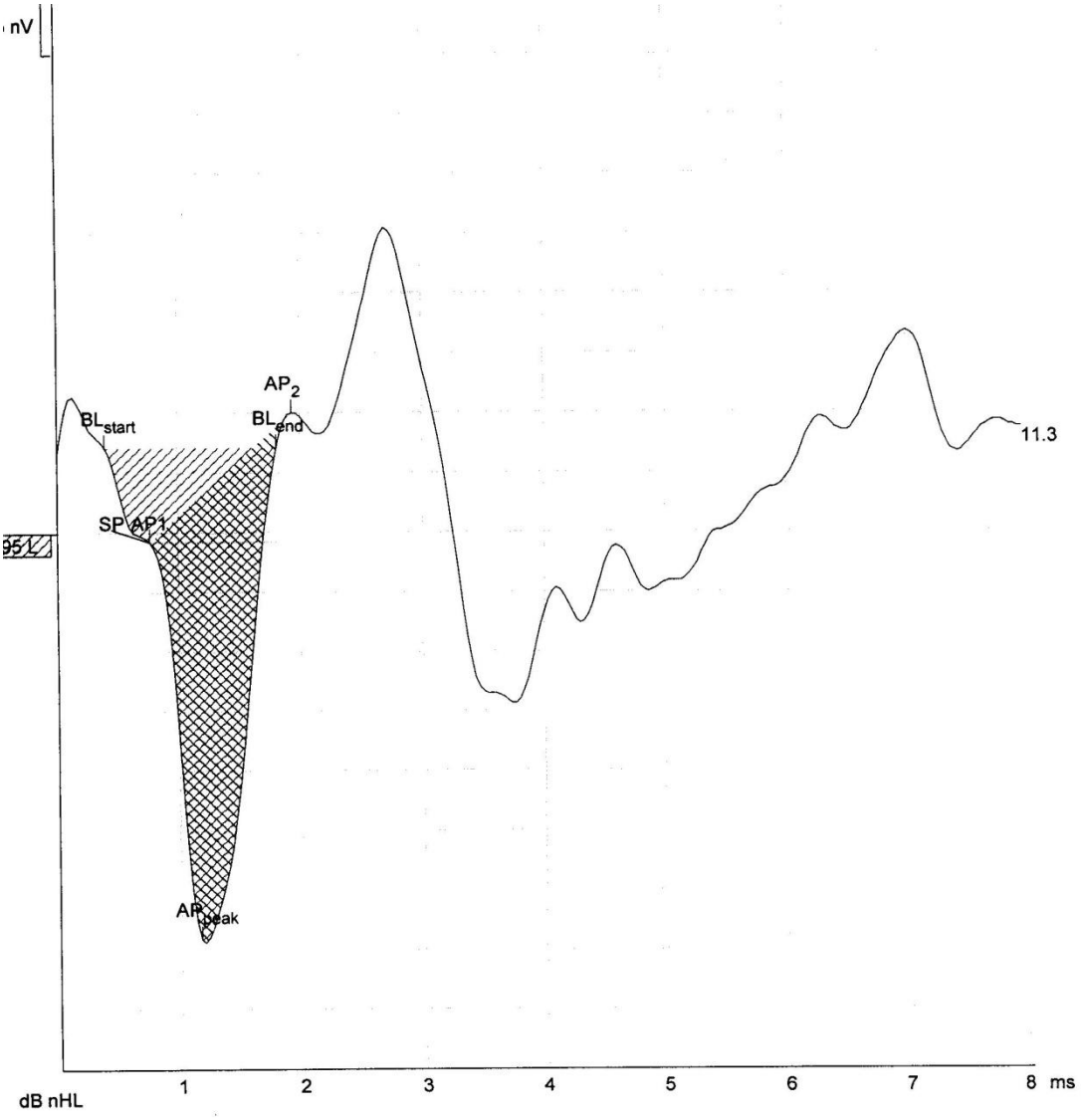

Figure 21: left ear ECochG response for a click stimulus presented at 95 dB nHL for subject 18 first trial.

Table 16: ECochG outcomes for subject 18 first trial.

AP Amp	SP Area	SP Duration	AP Amplitude	AP area	AP Duration	SP/AP Area	SP/AP Amplitude
0.120	12.15	0.37	0.619	9.876	1.17	1.230	.194

Figure 22: Left ear TM image for subject 18 prior to ECochG recording in the second trial.

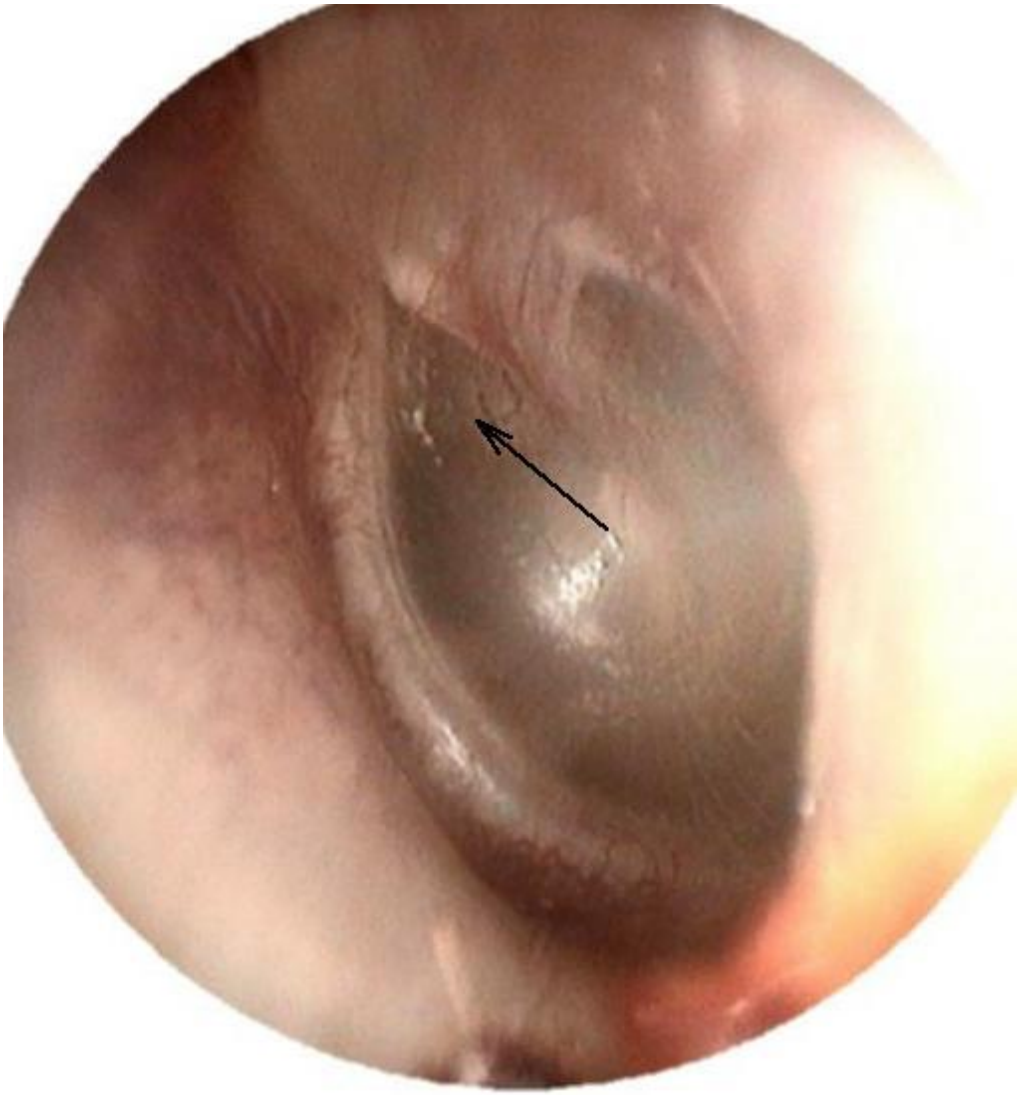

Figure 23: Left ear TM image for subject 18 after ECochG recording in the second trial. Gel marker was located in anterior superior quadrant of the TM.

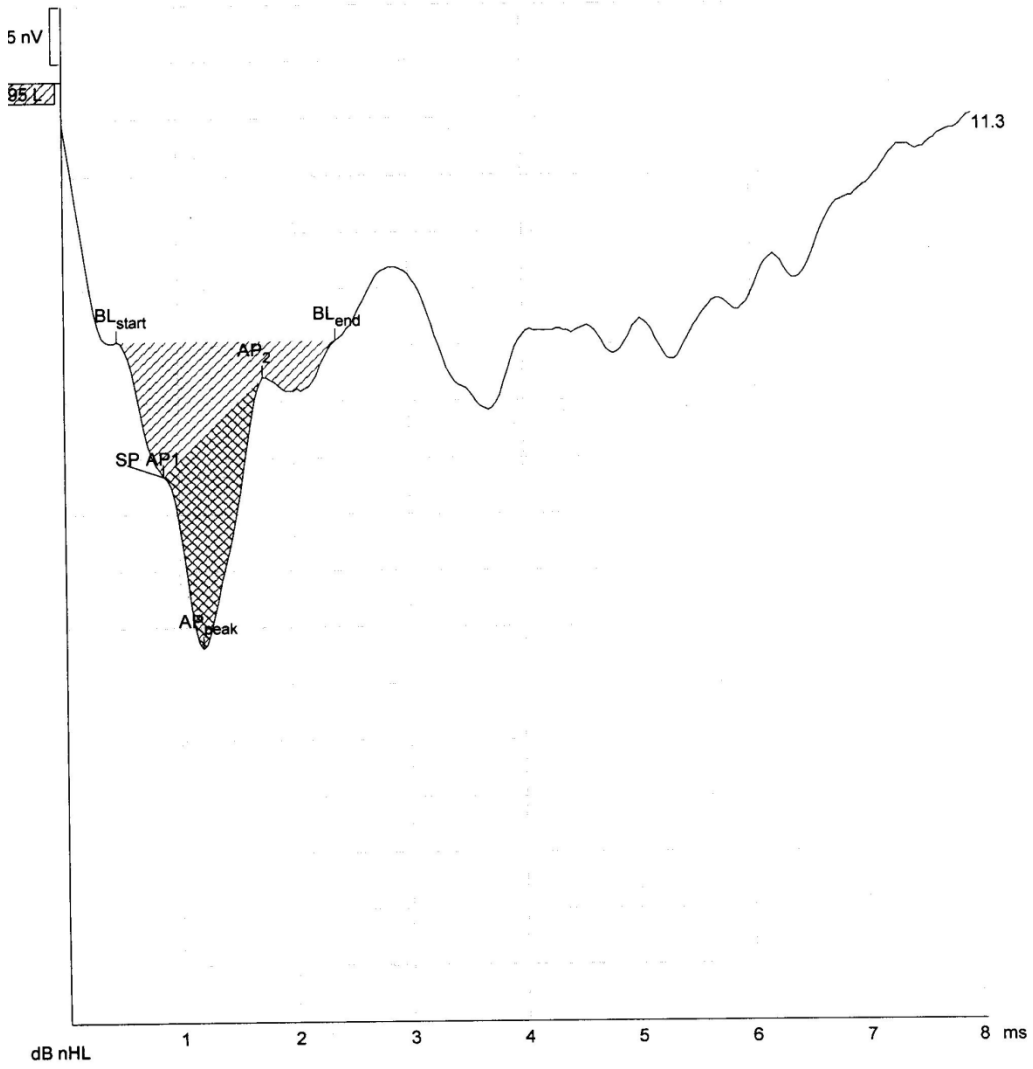

Figure24: ECochG response for a click stimulus presented at 95 dBnHL for subject 18 in the second trial.

Table 17: ECochG outcomes for subject 18 second trial.

SP Amp	SP Area	AP Amp	AP Area	AP Duration	SP Duration	SP/AP Area	SP/AP Amp
0.179	**8.705**	**.409**	**3.745**	**0.87**	**0.409**	**2.324**	**.437**

E – Effect of the angle, the length and the marker's area size on the SP/AP area ratio.

As described earlier in the manuscript ,the SP/AP amplitude ratio is the most commonly used measurement in the diagnosis of MD, but many studies (e.g. Sass, Densert, Magnusson, and Whitaker, 1997; Devaiah, Dawson, Ferraro, and Ator, 2003) have reported a sensitivity value for this parameter of 55%-65% in the diagnosis of MD. ECochG's low sensitivity has encouraged many researchers to find other approaches to increase the test sensitivity. One of these approaches focused on combining both the amplitude and duration of SP and AP parameters to measure the area of the SP-AP complex (Ferraro and Tibbils, 1999). In another study Almomani et al (2006) found that when SP/AP area ratio and SP/AP amplitude ratio are used together the sensitivity of ECochG as a diagnostic test for MD improves to 92%.

A mixed-effect regression model was conducted to investigate the effect of the angle and the marker's area size on the SP/AP area ratio. Our regression model is $Y= \beta0+\beta1X1+\beta2X2+ \beta3X3+\varepsilon$. Where Y is the SP/AP area ratio, β0 is a random intercept, X1 is the angle, X2 is the length, X3 is the marker's area size, and ε is a random error. Our results revealed no significant effect of the marker's area size or the length across all the measurements on the SP/AP area ratio. Also, results revealed a significant effect of the angle of the marker on the SP/AP area ratio (P=.031) with a regression coefficient estimate of -.002144μv.ms/degree. This means in every one degree angle increase,the SP/AP area ratio decreased by 0.002144 μv.ms . Our model suggests that the largest SP/AP area ratio will be in the superior anterior quadrant while the smallest will be on the inferior anterior quadrant of the TM. For example, based on our model SP/AP area ratio = β1.X1 where β1= - 0.002144 and X1 is the marker's angle. If one of our subjects has a marker's angle of 139 degree at the first trial and the SP/AP area ratio was

1.188μV.ms. At the second trial his marker's angle was 344 degree. According to our model his SP/AP area ratio= the difference in the angle between the second trail and the first trial = 344-139= 205 degrees. If we fit that in our model, SP/AP for second trail = (-0.002144x 205) + 1.188= 0.748μV.ms. That means the SP/AP area ratio will decrease by 0.44μV.ms in the second trail compared to the first trial. But this model does not apply to all subjects. For example, subject number three had a marker's angle of 139 at the first trial and SP/AP area ratio of 1.188. In the second trail he had a marker's angle of 344 degree but his SP/AP area ratio was 1.621.

As indicated above, our results showed that 68% of the time the electrode location was on the posterior superior quadrant. Also as described above, ear canal morphology played a role in placing the electrode at the same quadrants, and we had no control over placing the electrode on the TM. Therefore, comparisons of the SP/AP area ratio between the four quadrants were invalid due to small number of data points from quadrants other than the posterior-inferior one.

We speculate that the variability of the SP/AP area ratio associated with the variations of the tymptrode is due to two factors. First is the mass of the electrode against the TM, since we are using a broadband click stimulus, this factor is not a big contributor to the variability, especially if we know that mass mostly affects the low frequencies and our stimulus is more high frequency specific. A click has all frequencies, when it passes through the transducer, the signal will be the spectrum of the transducer. Second is the stiffness that we added to the system when we placed the electrode on the TM. The location where we added the stiffness on the TM might affect the vibration of the TM, and might cause some variability in the response, since stiffness facilitates the transmission of higher frequencies.

Most importantly, although our results showed that the marker's angle statistically affected the SP/AP area ratio, this effect was not clinically important. We previously defined our upper normal limit for SP/AP area ratio as 2.36. There was only one observation above this normal limit for subject number 6. It seems that the increase in the SP/AP area ratio was not associated with the angle of the marker, because in the first trial the angle of the marker was 71 degrees, and the SP/AP area ratio was 2.693. While in the third trial the angle was 98 degrees and the SP/AP area ratio was.988. According to our model, the angle differences between the two trials were 98-71=27 degrees. The SP/AP differences between the two trials should be 27x.002144= .058 μV.ms. That means the differences in SP/AP area ratios between the two trials were not only due to the location of the electrode.

Although our model indicated a statistically significant effect of the marker's angle on the SP/AP, clinically there were no significantly important differences of the TM electrode variations on the SP/AP area ratio.

Chapter VI

Summary and Conclusions

The main findings of this study are:

1) 68% of the time the TM electrode sits on the posterior superior quadrant of the TM when placed blindly, as in standard clinical procedure.
2) In some cases ear canal morphology played a role in where the electrode was seated on the TM.
3) There was significant variation of the tymptrode location on the four quadrants of TM across all the trials.
4) There was no significant variation of the tymptrode location on the area between the center and the edge of the TM.
5) There was no significant variation between the marker's area sizes across all the measurements.
6) The variations of the tymptrode location across the four quadrants of the TM had no significant effect statistically or clinically on the SP/AP amplitude ratio.
7) Although the variations of the tymptrode location across the four quadrants of the TM had a statistically significant effect on the SP/AP area ratio, theses effects were not clinically important.

Overall Conclusion:

Variations of the tymptrode location on the TM had no clinically important effects on the outcome of an ECochG exam in normally hearing subjects.

Recommendations for future research:

ECochG is a valuable tool in the diagnosis of MD. Since the population in this study was normal hearing adults, additional research regarding the effect of variations in electrode placement targeting the MD population with large SP/AP area and amplitude ratios is needed.

Also, the variations in ECochG recording and measurement parameters are obvious in the literature. Many studies are hesitant to report ranges for the different ECochG parameters due to lack of standardization among clinicians in performing ECochG (e.g., stimulus type and level, measurement protocols, calibration). Therefore, standardization of recording and measurement protocols for ECochG remains an important goal of future research in this area.

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Appendix A

Raw Data

Subjects	Measu	MR area	Length	Angle	SP/AP amplitude	SP/AP Area
1	1	0.008	0.16	68	0.142	1.669
1	2	0.1	0.53	147	0.102	1.779
1	3	0.149	0.122	144	0.067	1.418
2	1	0.022	0.444	230	0.16	1.103
2	2	0.327	0.122	250	0.119	0.691
2	3	0.448	0.088	16	-999	-999
3	1	0.05	0.466	139	0.169	1.188
3	2	0.048	0.163	344	0.116	1.621
3	3	0.35	0.044	183	0.226	1.191
4	1	0.03	0.235	178	0.225	1.579
4	2	0.077	0.202	195	0.051	1.16
4	3	0.035	0.252	178	0.219	1.129
5	1	0.107	0.191	342	0.101	1.037
5	2	0.099	0.212	346	0.084	1.027
5	3	0.16	0.091	168	0.273	1.318
6	1	0.5	0.09	71	0.238	2.693
6	2	0.072	0.324	174	0.017	2.273
6	3	0.84	0.309	98	0.008	0.988
7	1	0.351	0.29	97	0.194	1.23
7	3	0.125	0.104	82	0.142	1.632
8	1	0.014	0.301	159	0.058	1.567
8	2	0.07	0.493	139	0.088	1.48
8	3	0.12	0.43	126	0.15	2.163
9	1	0.22	0.064	159	0.014	1.508
9	2	0.249	0.211	92	0.172	1.569
9	3	0.325	0.222	126	0.174	1.493
10	1	0.087	0.39	152	0.188	1.936
10	2	0.111	0.366	157	-999	-999
10	3	0.109	0.379	150	0.069	1.159
11	1	0.382	0.538	148	0.311	1.496
11	2	0.143	0.403	162	0.33	1.724
11	3	0.268	0.275	125	-999	-999
12	1	0.127	0.328	147	0.17	0.98
12	2	0.042	0.278	145	0.045	1.004
12	3	0.036	0.371	159	0.123	1.848
13	1	0.081	0.339	175	0.119	1.49
13	2	0.061	0.399	185	0.131	1.326

Subjects	Measu	MR area	Length	Angle	SP/AP amplitude	SP/AP Area
13	3	0.145	0.38	112	0.073	1.769
14	1	0.282	0.105	162	0.087	1.516
14	2	0.064	0.487	114	0.177	1.996
14	3	0.101	0.4	164	0.007	1.442
15	1	0.043	0.4	113	0.064	1.061
15	2	0.025	0.165	347	0.181	1.479
16	1	0.009	0.397	119	0.198	1.545
16	2	0.2	0.466	79	0.31	2.3
17	1	0.072	0.34	156	0.186	2.209
17	2	0.044	0.471	168	0.351	1.442
17	3	0.086	0.314	185	0.187	1.197
18	1	0.018	0.441	76	0.119	1.515
18	2	0.016	0.125	198	0.437	2.324

Appendix B

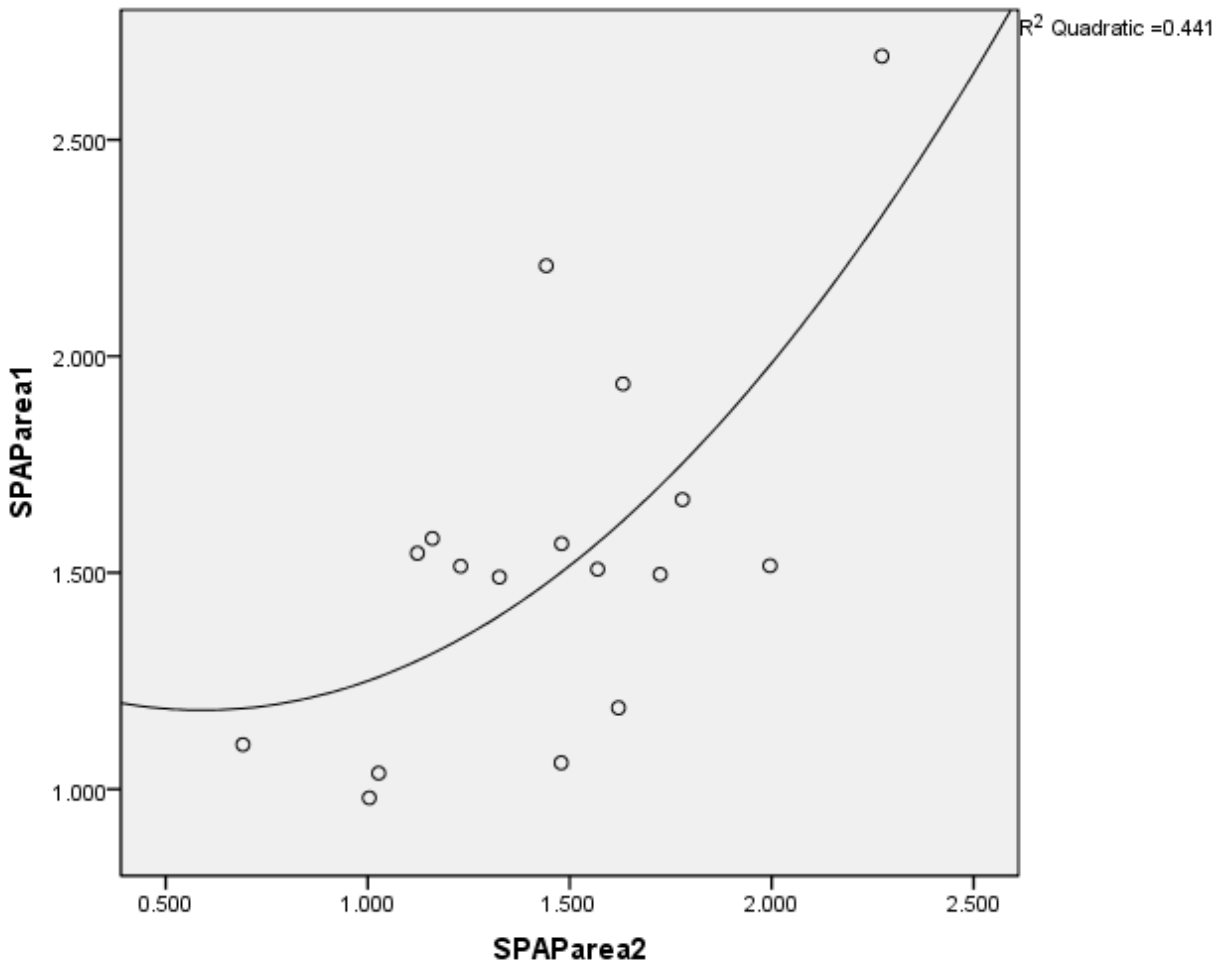

Figure 25: A scatter plot represents the relationship between SP/AP area ratio for first and second trials

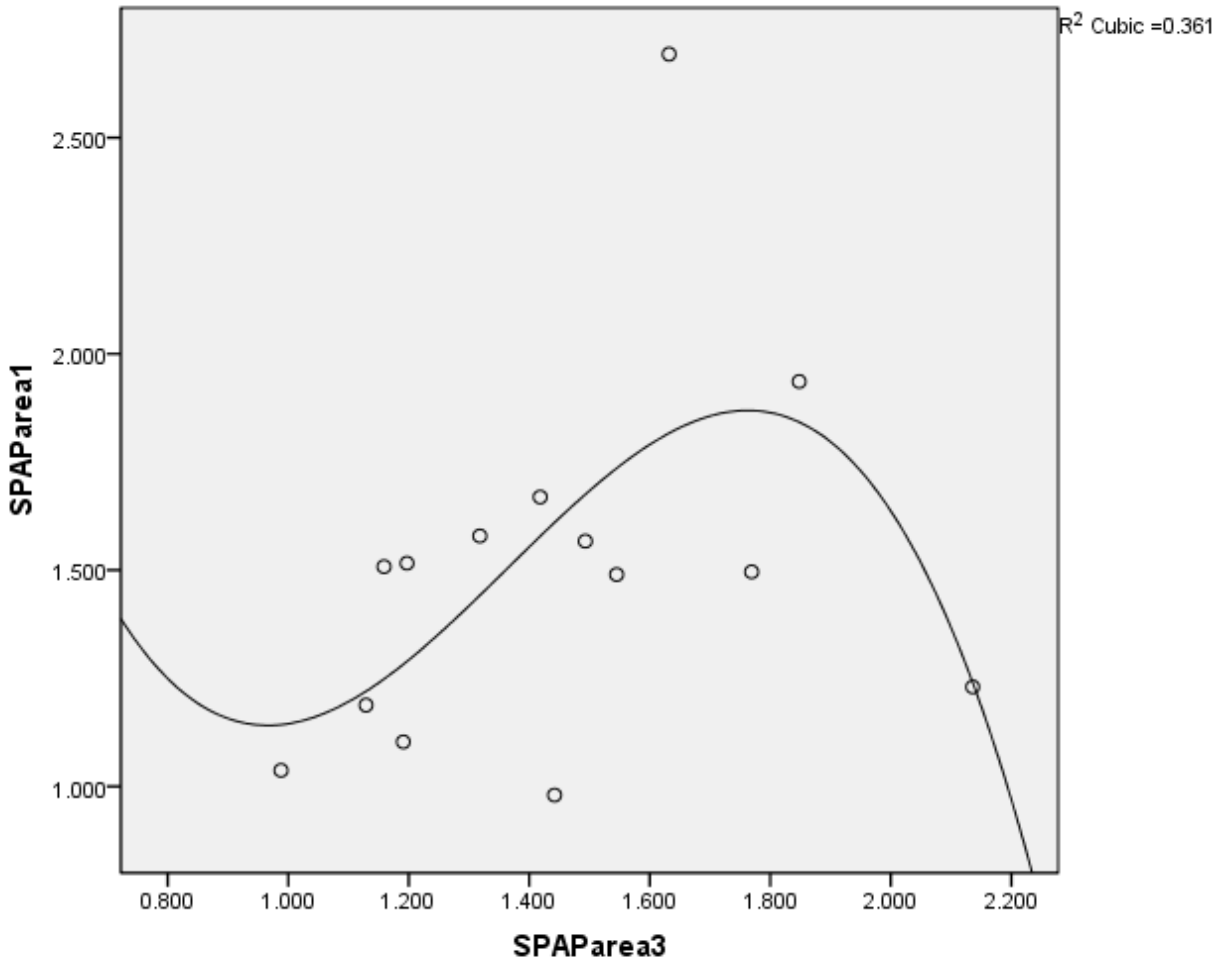

Figure 26: A scatter plot represents the relationship between SP/AP area for trial one and trial three

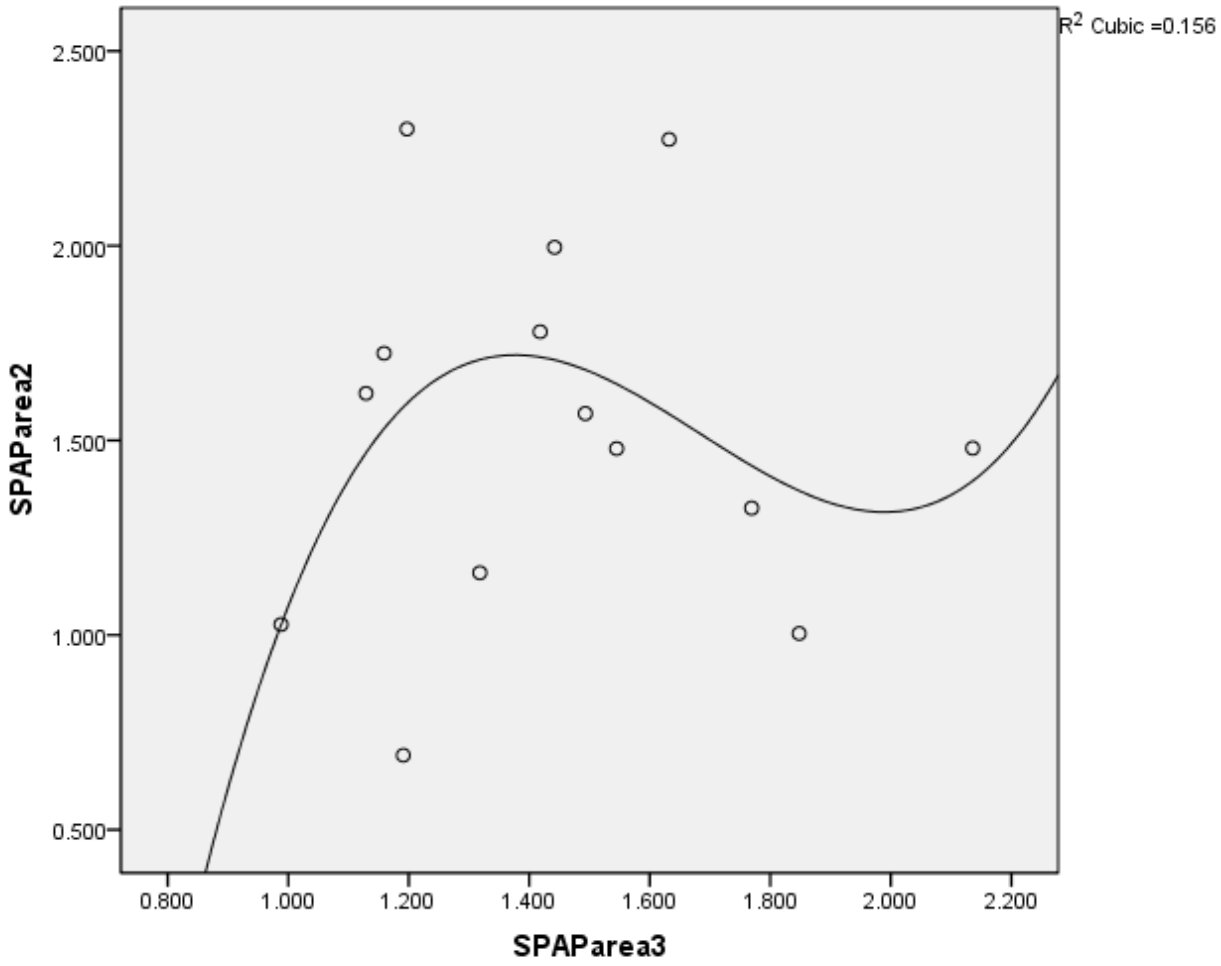

Figure 27: A scatter plot represents the relationship between the SP/AP area ratios for trial two and trial three.

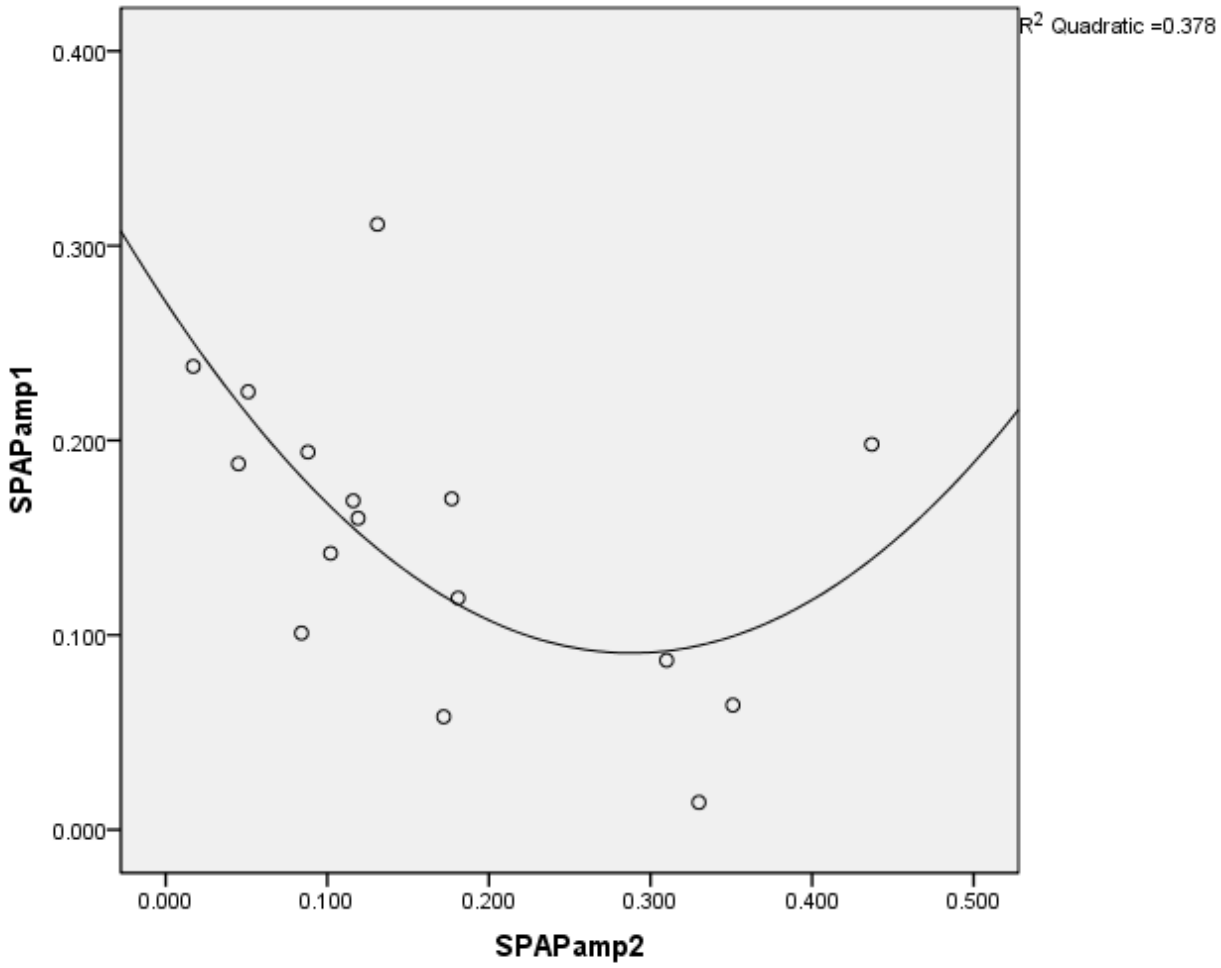

Figure 28: A scatter plot represents the relationship between SP/AP amplitude ratios for trial one and trial two.

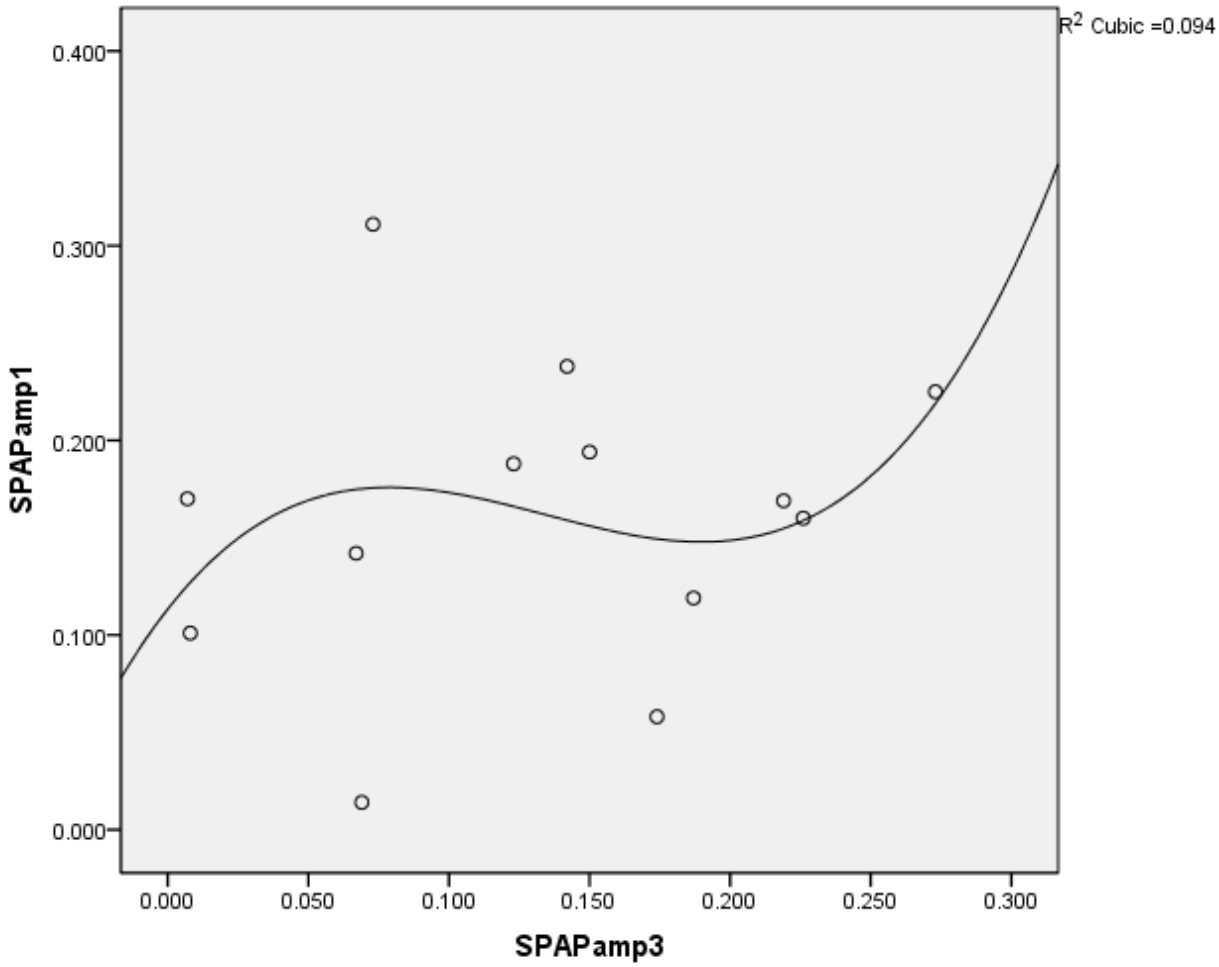

Figure 29: A scatter plot represents the relationship between the SP/AP amplitude ratios for trial one and trial three.

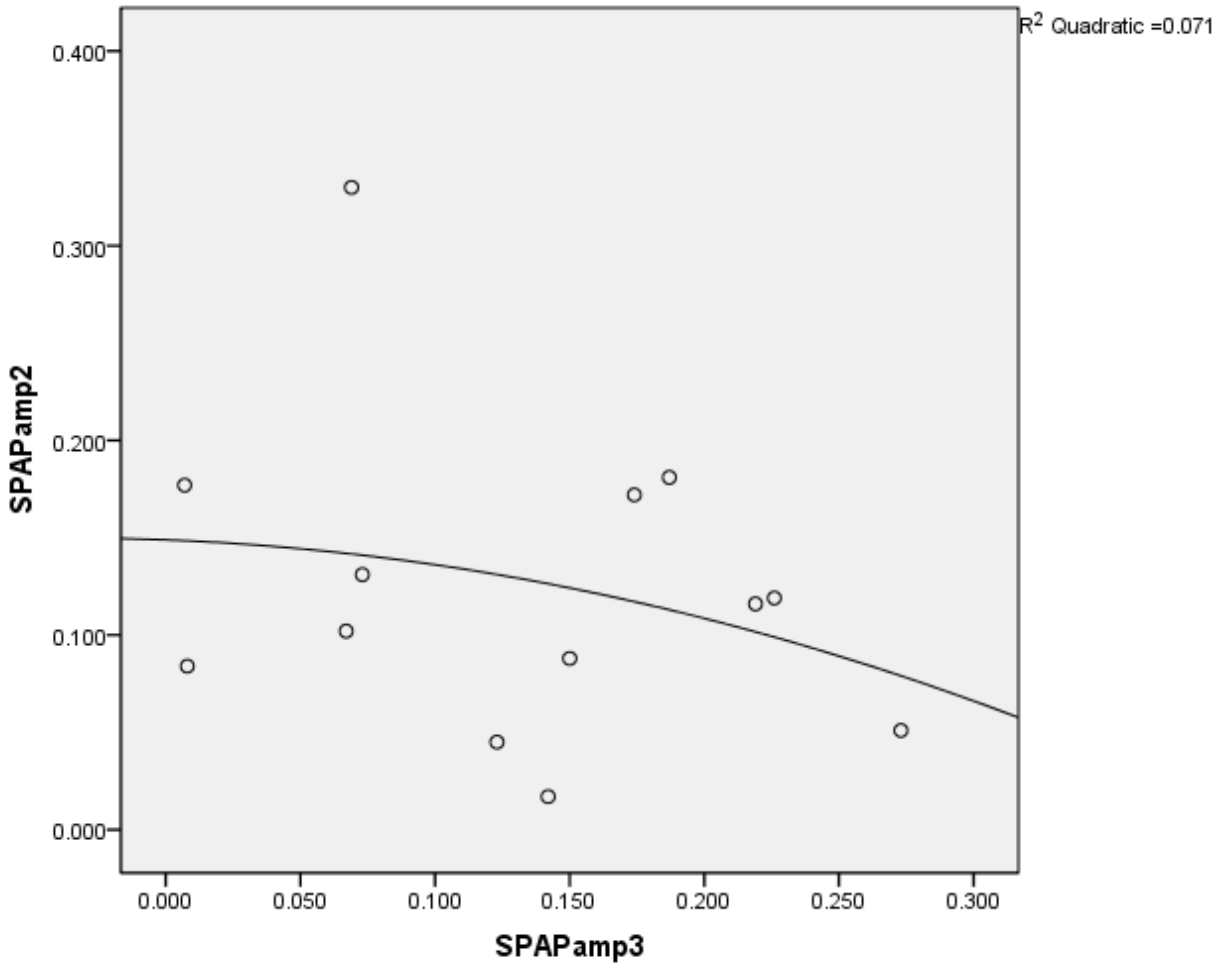

Figure 30: A scatter plot represents the relationship between SP/AP amplitude ratios for trial two and trial three.

Appendix C

CONSENT
FORM

Electrocochleographic Recordings from the Eardrum: Variation and Effect of Electrode Location in Normal Subjects

Protocol No.: Sponsor John Ferraro, Ph.D.

Introduction

As a person with normal hearing and no current or previous ear illness or disorder, you are being asked to participate in a research study about variation of electrode location on normal hearing subjects.

Your participation is voluntary, and you may change your mind at any time. There will be no penalty to you if you decide not to participate, or if you start the study and decide to stop early. Choosing not to participate in this study will in no way affect your employment or student status here at KUMC.

This consent form explains what you will be doing if you are in the study. It also describes the possible risks and benefits. Please read the form carefully and ask as many questions as needed before deciding to participate in this research.

You can ask questions now or anytime during the study. The researchers will tell you if they receive any new information that might cause you to change your mind about participating.

This research study will take place at the University of Kansas Medical Center (KUMC) under the direction of John Ferraro, Ph.D. as the principle investigator, and Mohammad Alhanada, Ph.D. student, as a secondary investigator. Approximately ten subjects will participate in the study.

BACKGROUND

Electrocochleography (ECochG) is a procedure used to record the electrical responses of the inner ear (cochlea) and the auditory nerve. ECochG has been used as an objective method to help diagnose Meniere's Disease (MD). MD is a disorder associated with the inner ear characterized by frequent episodesof dizziness, fluctuating hearing loss, ear fullness, and tinnitus.

PURPOS
E
The purpose of this study is to observe the variation of electrode location associated

Rev. June 2009
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Approval Date: 8/8/11 to 8/7/12

with the recording ECochG from the ear drum in adult subjects with normal hearing. And to investigate the effect of these variations (if any) on the resultant recording.

PROCEDURES

If you are eligible, and decide to participate in this study, you will be participating in two sessions. Each session will last approximately one hour. Sessions will be separated by one to seven days.

Your participation will involve the following procedures and tests:

1. Otoscopy: This is the process of looking into your external ear canal with a video otoscope. A video otoscope is a small camera that is used to view and capture an image of the ear drum and ear canal. The front end of the camera has a disposable plastic ear tip that is placed at the entrance to the ear canal. An image of the drum and ear canal will be captured prior and after each ECochG recording. The image will be stored in a computer. This procedure should take about five minutes each time it is performed.

2. Tympanometry: a non-invasive and painless procedure used to determine how your middle ear works when we present a sound into your ear canal through a small probe seated in the entrance of the ear canal, and the small probe will also record the vibrations of the ear drum to this sound. The exam usually lasts about five minutes.

3. Electrocochleography (ECochG): a non-invasive and painless procedure for recording the electrical responses of the inner ear and hearing nerve. This test involves the placement of four, disposable surface electrodes: two on the forehead and one on the scalp behind each ear, and a special rubber-tipped electrode on the external surface of the ear drum. This procedure should take about 40 minutes.

   During this procedure you will be comfortably seated on a reclined chair. Skin preparation includes cleaning small areas of the forehead and scalp (behind each ear) with an alcohol-soaked swab. Self-adhesive, disposable electrodes routinely used for ECochG testing will then be attached to these areas.

   Next, a special ear canal electrode designed for ECochG recording will be used. A conductive gel will be applied on the rubber tip of the electrode to insure proper electrical contact with the ear drum. Then, the electrode will be inserted along the ear canal and advanced until the soft, rubber tip rests against the outer surface of the ear drum. Once the electrode is placed, a small rubber plug connected via a tube to a small sound generator will be inserted into the entrance of the ear canal to hold the ECochG electrode in place and also deliver click-type sounds to the ear. These sounds excite the inner ear and hearing nerve to send electrical responses to the

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brain as all sounds do). The special electrode on the ear drum and the other electrodes on the forehead and scalp record these responses and deliver them to a special computer that stores and displays them for analysis. After ECochG recording is done, the rubber plug will be removed, and the ear drum electrode will be gently pulled out and removed from the ear canal. Also the forehead and scalp electrodes will be removed.

RISKS

All research procedures in this study are noninvasive in nature and there have been no significant injuries reported in previous procedures. Discomfort from the rubber tip of the electrode touching the ear drum may occur. If this discomfort is bothersome, the test will be terminated. Your ear drum will not be harmed or punctured and there is no risk of hearing loss. However, there may be some risks that have not yet been identified. Additionally, unexpected side effects that have not been previously observed may occur. Nevertheless, you should tell the research team about anything that is bothering you.

NEW INFORMATION

You will be told about anything new that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS

You are unlikely to benefit from participating in this study. However, researchers hope that the information from this study may be useful in the diagnosis and treatment of patients with MD and other inner ear disorders.

ALTERNATIVES

Participation in this study is voluntary. Deciding not to participate will have no effect on the care or services you receive at University of Kansas Medical Center or on your employment or student status in any way.

COSTS

There are no costs for participating in this study.

PAYMENT TO SUBJECTS

There is no payment for participation in this study.

IN THE EVENT OF INJURY

If you have a bodily injury as a result of participating in this study, treatment will be provided for you at the usual charge. Treatment may include first aid, emergency care and follow-up care, as needed. Claims will be submitted to your health insurance policy, your government program, or other third party, but you will be billed for the costs that are not covered by insurance. You do not give up any legal rights by signing this form.

INSTITUTIONAL DISCLAIMER STATEMENT

If you think you have been harmed as a result of participating in research at the University of Kansas Medical Center, you should contact the Director, Human Research Protection Program, Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160. Under certain conditions, Kansas State law or the Kansas Tort Claims Act may allow for payment to persons who are injured in research at KUMC.

CONFIDENTIALITY AND PRIVACY AUTHORIZATION

The researchers will protect your information, as required by law. Absolute confidentiality cannot be guaranteed because persons outside the study team may need to look at your study records. Your health information is protected by a federal privacy law called HIPAA. By signing this consent form, you are giving permission for KUMC to use and share your health information. If you decide not to sign the form, you cannot be in the study.

The researchers will only use and share information that is needed for the study. To do the study, they will collect health information from the study activities. You may be identified by information such as name, address, phone, date of birth, social security number, or other identifiers. Your health information will be used at KUMC by John Ferraro, Ph.D., Mohammad Alhanada Ph.D. student, members of the research team, the KUMC Research Institute, and officials at KUMC who oversee research, including members of the KUMC Human Subjects Committee and other committees and offices that review and monitor research studies.

All study information that is sent outside KUMC will have your name and other identifying characteristics removed, so that your identity will not be known. Because indentifying information will be removed, your health information will not be re-disclosed by outside persons or groups and will not lose its federal privacy protection.

Your permission to use and share your health information will not expire until the study is complete and the results are analyzed. After that time, information that personally identifies you will be removed from the study records.

The researchers may publish the results of the study. If they do, they will only discuss group results. Your name will not be used in any publication or presentation about the study.

QUESTIONS

Before you sign this form, John Ferraro, Ph.D. and Mohammad Alhanada, Ph.D. student should answer all of your questions. You can talk to the researchers if you have any more questions, suggestions, concerns, or complaints after signing this form. If you have any questions about your rights as a research subject, or if you want to talk with someone who is not involved in the study, you may call the Human Subjects Committee at (913) 588-1240. You may also write the Human Subjects Committee at Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160.

SUBJECT RIGHTS AND WITHDRAWAL FROM THE STUDY

You may withdraw your participation in this study at any time. Your decision withdraw will not prevent you from obtaining treatment or services at KUMC.

You have the right to cancel your permission for researchers to use your health information. If you want to cancel your permission, please write to John Ferraro, Ph.D. The mailing address is John Ferraro, Ph.D., University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160. If you cancel permission to use your health information, you will be withdrawn from the study. The researchers will stop collecting any additional information about you. They may use and share information that was gathered before your cancellation was received.

Additionally, this study may be stopped, without your consent, by the investigator. Your participation may also be stopped if it is in your best interest or if you do not follow the study requirements.

CONSENT

By signing this consent form, you agree that John Ferraro, Ph.D. and Mohammad Alhanada, Ph.D. student have given you information about this research study. They have explained what will be done and how long it will take. They have explained any inconvenience, discomfort or risks that may be experienced during this study.

By signing this form, you are saying that you freely and voluntarily consent to participate in this research study. You have read the information and had your questions answered.

You will be given a signed copy of the consent form to keep for your records.

_____
Type/Print Participant's Name

_____ _____ _____
Signature of Participant Time Date

_____
Type/Print Name of Person Obtaining Consent

_____ _____ _____
Signature of Person Obtaining Consent Time Date

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Approval Date: 8/8/11to 8/7/12