Functional Measurements of Ear Pathology in Patients and Cadaveric Preparations

by

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Submitted to the Harvard-MIT Division of Health Sciences and Technology in partial fulfillment of the requirements for the degree of

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Abstract

This work investigated the utility of reflectance ($R$), a measure of middle-ear mobility, in the differential diagnosis of pathologies responsible for conductive hearing loss (CHL). Current clinical practice cannot distinguish the multiple pathologies that produce conductive hearing loss in patients with an intact tympanic membrane and a well-aerated middle ear. The lack of a more effective non-surgical diagnostic procedure leads to unnecessary surgery and limits the accuracy of information available during pre-surgical consultations with the patient. A non-invasive measurement to determine the pathology responsible for a conductive hearing loss prior to surgery would be of great value.

This work focuses on determining whether a non-invasive diagnostic method, $R$, is a possible solution to this problem. Reflectance is a measure of the amount of sound that is reflected back when a sound stimulus is played in the ear canal. Measurements of $R$ were made in a large number of patients who had a variety of pathologies that cause CHL including ossicular fixations, disarticulations, and third window disorders in order to explore the clinical utility of $R$ measurements in differentiating these pathologies. Measurements of ossicular motion using laser Doppler vibrometry were also made in the same patients in order to compare the diagnostic utility of this well studied method to that of $R$. Using this patient information, multiple diagnostic uses and possibilities were explored, which showed the pre-surgical diagnoses of various pathologies.

In order to investigate the effects of these pathologies in a controlled and systematic way, $R$ and other metrics of middle-ear performance were also measured in human temporal bone preparations with simulated pathologies similar to those in the patient populations. Reflectance was also measured up to a higher frequency than had previously been possible using an experimental acoustic reflectance measurement system. We then analyzed the extended frequency measurements in novel ways to determine the effects of pathology on the time-domain characteristics.
The high-frequency measurements in temporal bones were then used to explore potentially diagnostically useful computational models of middle-ear mechanical function in normal and pathological ears.

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Title: Assistant Professor of Otology and Laryngology, Harvard Medical School
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Chapter 1

Introduction

1.1 PROBLEM IDENTIFICATION

The causes of conductive hearing loss are often difficult to determine despite the frequent presentation of patients with various middle-ear diseases in the clinic (Merchant et al., 1998). The transmission of sound energy to the inner ear is affected by a wide range of factors that involve many segments of the peripheral auditory system: from the ear canal through structures within the inner ear. A pathological change anywhere within this sound transmission path can produce a 'conductive' hearing loss with similar audiometric measurements. Current clinical practice falls short in the differential diagnosis of patients with conductive hearing loss, an intact tympanic membrane, and a well-aerated middle ear. Conductive hearing losses in such middle ears are commonly associated with stapes immobilization (commonly called a 'fixation') due to otosclerosis, but can also be caused by a discontinuity in the ossicular chain, fixation of the malleus or incus, or a pathological opening in the bony inner ear wall such as a superior semicircular canal dehiscence. These inner-ear openings are called 'third window' pathologies because they – like the normally occurring oval and round windows – are low-impedance paths for sound energy to flow into and out of the cochlea. In common practice, precise determination of the cause of a conductive hearing loss is not achieved without exploratory middle-ear surgery (Merchant and Rosowski, 2010). A non-invasive measurement that objectively distinguishes among possible ossicular and inner-ear pathologies would be of value as it would (1) aid in preoperative counseling and pre-surgical planning, (2) prevent unnecessary middle-ear surgery in cases of patients with third window pathologies, and (3) help screen patients who should be referred for further testing such as a high resolution computed tomography (CT) scan and vestibular evoked myogenic potential (VEMP).
testing. Furthermore, a sensitive mechanical indicator of the presence of a canal dehiscence, even in the absence of any hearing loss, would be a useful part of the diagnostic workup for these bony defects.

Otologic clinical practice makes limited use of objective assessments of middle-ear mobility to aid the diagnosis of middle- and inner-ear disease. A common measurement is 226 Hz tympanometry, which is a sensitive and selective indicator of non-aeration of the middle ear and perforation of the tympanic membrane but is a poor indicator of ossicular disorders. Current work indicates that more sophisticated measurements of middle-ear mobility will aid in the differential diagnosis of middle-ear disease, particularly measurements that consider mechanical responses over a wide range of stimulus frequencies (Prieve et al. 2013; Nakajima et al., 2013; Nakajima et al., 2012; Rosowski et al., 2012; Voss et al., 2012; Shahnaz et al., 2009; Feeney et al., 2009; Rosowski et al., 2008; Allen et al., 2005; Feeney et al., 2004; Margolis et al., 1999).

1.2 PRIOR WORK AND GOALS

Measurements of umbo velocity (UV) using laser-Doppler vibrometry have been shown to aid in the non-invasive diagnosis of middle-ear disorders. Umbo velocity measurements use a laser-Doppler vibrometer directed through the ear canal and focused at a naturally-reflective location near the umbo (the distal tip of the malleus attached near the center of the tympanic membrane) while moderate levels of sound stimulate the ear. These measurements have been characterized in the ears of normal subjects, as well as in ears of patients with: (i) stapes or malleus fixations, (ii) ossicular discontinuity, and (iii) superior semicircular canal dehiscence (SCD) (Rosowski et al., 2008, Whittemore et al., 2004, Rosowski et al., 2003). Similar measurements have also been performed in cadaveric human temporal bone preparations that simulate various middle-ear pathologies (Chien et al., 2007, Nakajima et al., 2005).
Whittemore et al (2004) established baseline normal measurements of UV using laser Doppler vibrometry in 56 normal hearing adults as well as in 47 subjects with sensorineural hearing loss (SNHL). No differences were found as a result of SNHL. Additionally, no significant effects of stimulus level, ear side (left or right ear), gender, or age were found.

Rosowski et al (2008) measured UV in 78 ears with confirmed ossicular pathologies: 57 with stapes fixation, 5 with malleus fixation, and 16 with either partial or complete discontinuity. The authors found that the combination of UV measurements and audiometric data (i.e. the difference between air- and bone-conducted auditory thresholds) separated the different pathologies. These results are supported by data from a human temporal bone preparation, which simulated ossicular fixations (Nakajima et al., 2005). Changes in the UV from initial measurements on the temporal bone were observed as a result of ossicular fixations of the malleus, incus, and stapes.

Umbo velocity has been shown to aid in differential diagnosis of ossicular pathologies, and is also useful in the diagnosis of the conductive hearing loss caused by inner-ear third window pathologies, such as SCD. Rosowski et al (2008) showed that the combination of UV and audiometry distinguished SCD from other ossicular pathologies causing conductive hearing loss. Additionally, Chien et al (2007) studied the effects of SCD in a temporal bone preparation and also found differences in UV as a result of SCD.

While UV is a useful research tool that can help differentiate between different causes of conductive hearing loss, there are substantial limitations to its use in the clinic. Umbo velocity is not FDA approved for clinical use and the manufacturer of the laser-Doppler vibrometer has not pursued such approval. Umbo velocity measurements require a trained clinician to operate the device and precisely aim the laser at the umbo, while a second person runs the computerized measurement procedure. Thus a cost-effective easily useable non-invasive tool to aid in the
differential diagnosis of conductive pathology is still needed to prevent misdiagnoses, wrong treatments and unnecessary surgeries.

Reflectance \((R)\) is another non-invasive measure of middle-ear mobility over a wide sound frequency range that is being considered for the differential diagnosis of conductive pathologies. Unlike \(UV\) measurements, reflectance is measured using an FDA approved device that is simple to operate; however, it is yet to be determined if this device can aid the differential diagnosis of conductive pathologies. Pressure reflectance is calculated from a sound pressure measurement made in the ear canal in response to a controlled stimulus, and can be considered the complex ratio between the forward pressure wave that is presented in the ear-canal and the reflected pressure wave from the tympanic membrane (TM). Ear-canal pressure reflectance, or quantities directly related to it such as power reflectance \((PR)\), transmittance, and absorbance, have been characterized in normal ears (Keefe et al., 1993; Voss and Allen, 1994; Shahnaz and Bork 2006; Rosowski et al., 2012) and have also been examined as a function of development in newborns, children and adults (Keefe et al., 1993; Keefe and Levi, 1996; Keefe et al., 2000; Feeney and Sanford, 2004; Werner et al., 2010; Merchant et al., 2010).

Reflectance has also been measured in a few cases of specific middle-ear disorders including otitis media with effusion, otosclerosis, ossicular discontinuity, hypermobility of the tympanic membrane, and tympanic membrane perforation (Feeney et al., 2003; Allen et al., 2005; Shahnaz et al., 2009; Nakajima et al., 2012). Collectively, these data suggest that reflectance shows potential utility in the non-invasive differential diagnosis of these pathologies.

While a substantial number of \(R\) measurements have been collected on subjects and patients with various pathologies, there are limitations to these data. In most cases, the number of subjects with a given pathology is small, and while statistically significant differences from normal may be evident, much larger subject populations are needed to clearly evaluate the clinical significance in terms of its sensitivity and
selectivity in identifying different pathologies. Studies that have found statistical significance between pathological states as compared to normal (e.g. otosclerosis), show that there is considerable overlap of the individual recordings between those with pathology and normal. These overlaps make it unfeasible to determine pathology from normal by this method in a clinical setting (despite a statistical difference). Additionally, as mentioned above, the vast majority of the literature focuses on comparing reflectance measurements in diseased ears to those of normal-hearing ears. In the audiology and otology clinic, where hearing testing is the norm, patients with conductive-hearing loss are readily segregated from those with normal conductive function. Therefore, a significant question is whether there are features that separate the possible causes of the CHL from each other (not whether they are separable from normal hearing). The first goal of this work is to expand the current data set available on $R$ measurements in patients with middle-ear disorders, by characterizing and evaluating a large number of patients for each pathology of interest and determining the efficacy of $R$ in the differential diagnosis of these pathologies. This expands the patient data set and allows for a controlled comparison of $R$ in a larger population of patients with the range of pathologies that would be most useful in terms of a differential diagnostic.

Given the large intersubject variability seen in both $R$ and $UV$ in normal, healthy subjects (Keefe et al., 1993; Whittemore et al., 2004; Rosowski et al., 2012), knowledge of how the healthy normal ear responds, and then subsequently changes as a result of a specific pathology, would provide the most controlled assessment of the effects of various pathologies. While in patients, only measurements can be made after pathological change, human temporal bones offer the opportunity to begin with measurements on a normal preparation, with subsequent manipulations to simulate middle-ear disease, and reversal of the manipulation to ensure that measured changes were indeed caused by the manipulation.

Limited $R$ measurements have been made on temporal bone preparations simulating various middle-ear pathologies including positive and negative static
pressure, middle-ear fluid, fixations, ossicular discontinuity, and perforations (Feeney et al., 2009; Voss et al., 2012). One limitation of the previously published measurements of $R$ in temporal bone preparations is that no estimates of hearing loss resulting from the manipulations are provided (except for ossicular discontinuity (Feeney et al., 2009)). Additionally, no objective measure of the status of the preparation is provided. Healthy appearing temporal bone middle ears have been known to show abnormal ossicular velocities, and removal and preparation of a temporal bone for experimentation can, at times, result in air bubbles entering the cochlea, which can affect the mechanics of sound conduction (Ravicz et al., 2000). Laser-Doppler vibrometry can be used to determine the presence of normal sound-induced umbo, stapes and round-window velocity. The sound-induced motion of the stapes is one measure of the input to the cochlea, where manipulation-induced changes in stapes velocity ($SV$) can provide an estimate of the conductive hearing loss resulting from a given manipulation. Furthermore, comparisons of sound-induced round window and stapes velocities at low frequencies can aid in detection of the presence of air in the inner-ear, as the phase of the round window velocity is normally 180 degrees out of phase with the stapes velocity at low frequencies (Nakajima et al., 2005). Comparisons of umbo and stapes velocity with published normal measurements in human temporal bone preparations can also give information related to the status of the preparation, and indicate an abnormality that may not be detected by visual inspection, such as umbo velocity that is too high due to a discontinuity or too low due to increased stiffness (Rosowski et al., 2007).

Additionally, research utilizing $R$ in human temporal bone preparations have not studied SCD. Thus, the second goal of this work is to use a temporal bone preparation to make $R$ measurements while simulating various pathologies that cause conductive hearing loss, and to use laser Doppler vibrometry measurements at the umbo, stapes and round window to test the normality of the preparation, quantify the effect of a given manipulation on hearing loss, and compare results to previously published data in temporal bones (Chien et al., 2007, Nakajima et al., 2005) and patients (Rosowski, Nakajima and Merchant, 2008). Some of these
simulated pathologies can be reversed to confirm that changes are due to the previous manipulation alone (a useful control). A major difference between temporal bone and patient studies is that the former are commonly performed after modifying the middle-ear air spaces. We explored the effect of opening, closing and varying the dimensions of the middle-ear cavity on reflectance in our temporal bone preparation to assess how manipulations of the cavity structure impact the interpretation of our temporal bone data.

The third goal of this thesis is to measure $R$ at frequencies up to 20kHz in temporal bones and develop novel ways to analyze and characterize these measurements in order to evaluate the usefulness of the information at higher frequencies, both in the frequency domain and the time domain. Analysis of $R$ measurements have focused on assessing the data in the frequency domain over the 250 Hz to 6 kHz range, with minimal investigations as to how pathology affects $R$ at higher frequencies (> 6-8 kHz). Furthermore, analytic models describing middle-ear delay predict a temporal separation of different ossicular disorders that would be readily apparent in the impulse response, but there has been minimal experimental investigation of this potential temporal separation. Analyzing reflectance measurements in the time domain by observing impulse response of reflectance would be novel and possibly clinically useful. One reason for this lack of study is that current clinical reflectance measurement techniques are unable to deliver and measure accurate signals at frequencies above 6-8kHz (due to cross-talk between the stimulus and measurement channels). Measurements at higher frequencies provide the temporal resolution needed to tease out contributions of the ossicles to the impulse response (Siegel, 1995).

Finally, to increase our quantitative understanding of the changes in $R$ produced by manipulations of the ear’s conductive apparatus, and investigate the role the ear canal plays in determining $R$ at high frequencies, we investigate a few novel external and middle-ear models designed to describe the transmission of sound power through the external ear and power absorbance by the middle and inner ear.
Variations in model parameters fit to the normal and modified middle-ear data in multiple preparations are assessed for consistency and significance across the different preparations. We also attempt to use these model parameters to separate out the different manipulations, with the idea that correlations between manipulations and the fitted parameters may be of diagnostic utility.

The combination of information from measurements made in human patients, human temporal bone preparations, model simulations, and analyzing data by a new method utilizing high frequencies allow a thorough assessment of how these measurements change as a result of pathology, and show that there are distinguishing features between each pathology and the normal condition, as well as between the pathologies themselves. Such distinguishing features will allow us to develop reflectance-based tools to aid in the differential diagnoses of these pathologies, the final goal of this work.

1.3 SPECIFIC AIMS

The goal of this work was to investigate the utility of reflectance, a measure of middle-ear mobility, in the differential diagnosis of pathologies responsible for conductive hearing loss (CHL). Current clinical practice cannot distinguish the multiple pathologies that can produce conductive hearing loss in patients with an intact tympanic membrane and a well-aerated middle ear. As it is difficult to determine the cause of the conductive hearing loss, surgeons often assume the defect is due to otosclerosis and perform exploratory middle-ear surgery to investigate the mobility of the ossicular chain. The lack of a more effective non-surgical diagnostic procedure has led to unnecessary surgery and limits accurate information during pre-surgical consultation with the patient. A non-invasive measurement to determine the pathology responsible for a conductive hearing loss prior to surgery would be of great value. This work focuses on determining whether a non-invasive diagnostic method, reflectance ($R$), is a possible solution to this problem.
Measurements of $R$ were made in conjunction with measurements of ossicular motion (umbro velocity, $UV$) to define the relationship and to compare the diagnostic utility between $R$ and $UV$ measurements in different pathological conditions. Direct comparisons of $R$ and $UV$ were performed in patients with independently-determined pathologies, as well as in the controlled environment of human temporal bone preparations that simulate various conductive pathologies.

**Aim 1:** This aim explores the clinical utility of $R$ to differentiate between various middle- and inner-ear diseases. Reflectance measurements have shown promise in the diagnosis of some middle-ear disorders, but have not been studied in a large and diverse clinical population. This work measured $R$ as well as $UV$ in patients with a conductive hearing loss caused by stapes fixation, malleus fixation, disarticulation of the ossicular chain, or a third-window disorder such as superior semicircular canal dehiscence (SCD: a pathology that causes various symptoms including vestibular dysfunction, hearing loss, or both in combination). This data determined how these pathologies affect $R$ when compared to normal as well as when compared to each other. We investigated 1) whether $R$ can predict the level and location of an ossicular fixation by showing a graded response dependent on the level of hearing loss, 2) whether $R$ can distinguish between partial and complete disarticulations, 3) whether $R$ differs in patients with SCD with and without CHL, and 4) whether $R$ is different before and after surgery in SCD patients. We also compared the diagnostic efficiency of $R$ to studies of $UV$ (Rosowski et al., 2008). Chapters 2 and 3 address this aim.

**Aim 2:** The second aim of this work explores the effect of various pathological conditions on $R$ using a human temporal bone preparation, and directly compared these measurements to measurements of ossicular motion using laser Doppler vibrometry. To study $R$ changes in a systematic and controlled manner and test hypotheses concerning the basic mechanisms underlying the different pathologies, selected pathological conditions were simulated in a temporal bone preparation.
Reflectance measurements as well as measurements of both $UV$ (to compare to previously published results on similar preparations) and stapes velocity ($SV$; to estimate the amount of conductive hearing loss caused by the pathology) were made before and after each manipulation, and when possible, in measurements repeated after the manipulations were reversed. Chapter 4 addresses this aim.

**Aim 3:** The third aim of this work is to use a novel approach to measure $R$ with a custom device that utilizes high-frequency signals and analyze $R$ in both the frequency domain and the time domain. This work investigates, for the first time, how various pathologies affect $R$ (1) at higher frequencies (> 6-8 kHz: as commercially available devices restrict their outputs to lower frequencies) and (2) in the time domain where the resolution of such temporal analyses is also limited by the high-frequency limit of existing devices. Using a new experimental system (the HARP System developed by JH Siegel), we measure $R$ up to 20 kHz in human temporal bone preparations similar to those in Aim 2, and develop novel ways to analyze and characterize these measurements. We determine whether high frequency $R$ information can be useful in differentiating pathologies, and whether conversion of the frequency-dependent reflectance to a time-domain reflectance (TDR) impulse response can aid in diagnosis. We also compared the measurements made with the HARP to measurements made using the FDA approved Mimosa $R$ system (which is used in Aims 1 & 2) in the same preparations up to the 6 kHz limit of that device. Chapter 5 addresses this aim.

**Aim 4:** The final aim of this work is to use the results in patients and temporal bones to refine and new models of the external and middle ear that simulate our $R$ results. Since these models all relate model structure to ear structures, quantifying the effect of 'pathological' changes in model structure tests hypotheses of how the different pathologies affect $R$ Chapter 6 addresses this aim.
1.4 REFERENCES


Chapter 2

Reflectance and Umbo Velocity Measurements in Normal Subjects and Patients with Conductive Hearing Loss

This chapter summarizes the results of two published reports (Rosowski et al and Nakajima et al. 2012). As a co-author in these reports I was responsible for much of the data gathering and the analysis of the reflectance data. Although, I did not conceive these studies, I was involved in all aspects of the work.

2.1 INTRODUCTION

Conductive hearing loss (defined as an air-bone gap on audiometry) in the presence of an intact, healthy tympanic membrane (TM) and an aerated middle ear is often seen in clinical practice and is most commonly due to fixation of the stapes, ossicular discontinuity, or a third window lesion of the inner ear such as superior semicircular canal dehiscence (SCD) (Merchant & Rosowski 2010). Currently, no diagnostic test exists that can reliably differentiate between the pathologic conditions described above. A diagnostic test that differentiates among these disorders and that can be used in an office setting would be of clinical value. Patients with a third window lesion would be spared unnecessary surgical exploration of the middle ear and pre-surgical knowledge of the type of ossicular pathology likely to be encountered at surgery (e.g., stapes fixation versus ossicular discontinuity) would help an otologist in preoperative counseling of patients regarding surgical risks and in preoperative planning.

Our group and others have demonstrated that umbo velocity (UV) measurement, coupled with audiometry, enables reliable pre-surgical differentiation among ossicular fixations, ossicular discontinuity and third window disorders [Goode et al. 1996; Rosowski et al. 2003; Rosowski et al. 2008]. That said, laser Doppler vibrometry (LDV) systems which measure UV that are commercially available are not FDA approved for clinical application, require a clinician with comfort and
experience in oto-microscopy, and are of relatively high cost (~$100,000 for the Polytec device). For these reasons, there is a limit to the clinical utility of UV measurements.

Reflectance ($R$) is a variation of clinical acoustic immittance testing that has been described by many investigators (Prieve et al. 2013; Nakajima et al. 2013; Nakajima et al. 2012; Rosowski et al. 2012; Keefe et al. 1993; Voss & Allen 1994; Puria & Allen 1998; Feeney et al. 2003). Power reflectance ($PR$), the square of the magnitude of $R$, is the fraction of the incident acoustic power that is reflected by the tympanic membrane back into the ear canal. $R$ measurements can be performed with a commercially-available, easy to use, relatively inexpensive device (~$10,000 for the Mimosa device) that received FDA approval in 2006 for clinical use. Power reflectance has shown promise in the differential diagnosis of some middle ear disorders. However, it has not been determined whether $PR$ can perform well in differentiating among various pathologies, as would be desired in a clinical setting.

The goal of this chapter was to investigate the clinical utility of $PR$ measurements in a population of patients with conductive hearing loss due to either stapes fixation, ossicular discontinuity, or SCD in the presence of an intact, healthy TM and an aerated middle ear and to compare these with measurements made on a population of strictly defined normal ears.

2.2 METHODS

2.2.1 Normal Subject Inclusion Criteria

Fifty-eight subjects were tested for the normative portion of the study, and informed consent and a brief medical and surgical history related to hearing were obtained. Umbo velocity ($UV$) and reflectance ($R$) measurements were made in a single session. In all subjects, pure-tone audiometric thresholds for air and bone conduction, in addition to 226 Hz tympanograms, were gathered in a separate
session by a certified audiologist. Out of the 58 subjects tested, 29 subjects (58 ears) met our criteria of “normal hearing, which had a criteria as follows:

(1) No history of significant middle ear disease (otitis media or effusion 2 or more years previously were not considered significant if there were no known residual consequences)
(2) No history of otologic surgery, with the exception of myringotomy or tympanostomy tube placement over 2 years prior.
(3) The external ear and TM revealed no abnormalities on otoscopic examination.
(4) Audiometric measurements had pure-tone thresholds of 20 dB HL or better at octave frequencies between 0.250 and 8 kHz.
(5) Air-bone gaps were no greater than 15 dB at 0.25 kHz and 10 dB between frequencies of 0.5 to 4 kHz. Most subjects had air and bone thresholds between 0 and 10 dBHL with an average near 8 to 9 dBHL at the highest frequencies.
(6) Tympanograms were Type-A peaked, with peak pressures of -100 to +50 daPa, static compliance of 0.3 to 2.0 cc, total tympanometric volumes (static compliance & ear canal volume) between 0.7 and 2.7 cc, and normal-appearing shape that is neither rounded nor sharp.
(7) All subjects included in the “normal hearing” population were required to have both ears fit the “normal” criteria.

2.2.2 Conductive Hearing Loss Patient Inclusion Criteria
Patients with conductive hearing loss, an intact tympanic membrane (TM) and aerated middle ear who have not had surgery were recruited from the Massachusetts Eye and Ear Infirmary otology clinic. This recruitment processes was aided by referrals from otologists in the clinic. UV and R measurements were made on 104 patients. A preliminary diagnosis of each patient is based upon testing done by the referring otologist. The final diagnosis is independently determined by surgery in the case of malleus fixation, stapes fixation, and ossicular discontinuity, while third-window pathologies are diagnosed by a combination of CT scan, signs
and symptoms, and other clinical tests, e.g. Vestibular Evoked Myogenic Potential testing and acoustic reflex (Mikulec et al. 2004). Patients are separated by final diagnosis into one of the four pathologic groups: malleus fixation, stapes fixation, ossicular discontinuity, or SCD. Ears with stapes fixation were included if the diagnosis was confirmed at subsequent surgery, and the post-stapedectomy air-bone gap was less than 10 dB averaged over the frequencies 500, 1000, and 2000 Hz (thus ensuring that other potentially confounding pathologies such as malleus fixation or a third window lesion were not responsible for some of the hearing loss). Ears with ossicular discontinuity were included if the diagnosis was confirmed at subsequent surgery. Ears with SCD were included if a high-resolution CT scan confirmed a dehiscence and if VEMP thresholds were abnormally sensitive [9].

Fourteen ears with stapes fixation due to otosclerosis, 6 ears with ossicular discontinuity (4 with complete and 2 with partial), and 11 ears with SCD met the criteria for inclusion and were analyzed in detail in the present study (a total of 31 ears). Among the 31 ears, the age range was 22 to 72 years; 15 were males and 16 were females. There were 11 right and 20 left ears. Of the 73 patients who were not included in this study, 19 patients did not have conductive hearing loss. History of previous surgery excluded 16 patients (8 tympanoplasty, 7 stapedectomy, and 1 mastoidectomy). Diagnosis was not confirmed in 22 patients (surgery had not been performed in 12 patients and postoperative air-bone gap did not close or follow-up did not occur in 10 patients). Nine patients had TM pathologies evident on otoscopy, 3 had mixed hearing loss with a large sensorineural component, and 4 were pediatric patients.

Measurements on all 31 ears included pure-tone audiometry for 0.25-8 kHz, \( R \) for 0.2-6 kHz at 60 dB SPL using the Mimosa Acoustics HearID system, and \( UV \) for 0.3-6 kHz at 70-90 dB SPL using the HLV-1000 laser Doppler vibrometer (Polytec Inc). In addition, 28 out of 31 patients also had standard 220 Hz tympanometry, the exception being 3 ears with stapes fixation. We analyzed \( PR \) as well as the
transmittance \(10 \times \log_{10}[1-PR]\). Transmittance is the dB descriptor of the fraction of incident power that is absorbed.

### 2.2.3 Velocity Measurements

Laser Doppler Vibrometry is used to measure umbo velocity \((UV)\). A speculum is placed in the ear canal and the umbo is visualized with a surgical microscope. A glass-backed tube connected to an ER 3 earphone and ER7 microphone (Etymotic Research, Elk Grove, IL) is coupled to the speculum (Figure 2.1). The sound stimulus is a nine tone harmonic complex with a stimulus level between 70 and 90 dB SPL. The sound pressure in the ear canal is measured within 5 mm of the tympanic membrane. A laser beam from a HLV-1000 laser Doppler vibrometer (Polytec Inc) is focused on the anterior border of the umbo where there is generally a bright reflection of laser light. The laser had a power of <1 mW (US FDA Class II), had a minimum spot diameter of 100 µm. The normalized velocities are quantified by the ratio of the measured velocity to the measured sound pressure in the ear canal near the tympanic membrane and have units of velocity per sound pressure (mm s\(^{-1}\) Pa\(^{-1}\)).

![Figure 2.1: LDV measurement set-up in human patients.](image)
2.2.4 Reflectance Measurements

Pressure reflectance \( R \) is the complex ratio between the reflected pressure wave and the forward pressure wave propagating in a tube or ear canal. Pressure reflectance is related to the acoustic impedance at the measurement point, and the impedance is calculated from the sound pressure measurement made in the ear canal. Pressure reflectance is related to impedance by the following equation:

\[
R(f) = \frac{Z}{\rho c / A} - 1
\]

\[
-\frac{Z}{\rho c / A} + 1
\]

where \( f \) is frequency, \( Z \) is the impedance looking into the ear canal, \( \rho \) is the density of air, \( c \) is the speed of sound in air, and \( A \) is the cross-sectional area of the ear canal at the measurement point. Power reflectance is then calculated as the square of the magnitude of the pressure reflectance, \( PR = |R|^2 \), and is a real number generally between 0 and 1, where 0 indicates that no energy is reflected and 1 indicates that all energy is reflected. In the case where the ear is actually generating sound power, e.g. in spontaneous acoustic emissions, \( PR \) may have a value greater than 1.0.

2.2.5 Calibration of Reflectance

Reflectance measurements are made using an Etymotic ER10C probe (containing a sound source and microphone) that is coupled acoustically to the ear canal using plastic tubing and a plastic foam tip, and coupled electrically to program controlled signal generation and measurement hardware (Mimosa Acoustics ®) along with the controlling software (HearID). To calculate the impedance in the ear canal, the Thévenin equivalent of the sound-delivery system and coupled foam ear tip is first estimated. To achieve this, a calibration is performed for every combination of foam tip and the ER10C prior to making measurements. Mimosa’s calibration procedure uses sound pressure measurements at the entrance of four cylindrical tubes of different lengths (Allen 1986; Voss & Allen 1994; Shahnaz & Bork 2006; Voss et al.)
2008). Mimosa's software requires the calculated Thévenin equivalent to be within a set of predetermined boundaries before one can proceed with reflectance measurements. "Poor" calibrations, as determined by these standards, could be caused by several reasons, which included poor coupling between the plastic tubing in the center of the foam tip and the foam tip itself, poor compression of the foam tip prior to insertion into the cylindrical tubes, and the inability for the foam tip to expand completely, allowing for small leaks. Calibrations for several foam tips were performed on the same day or day before subject measurements, and each tip was marked to identify its specific calibration measurement. Because of the uncertainties within the calibration process that sometimes led to many calibration trials before defining an adequate tip and calibration, it was impractical to calibrate immediately before each subject measurement.

2.2.6 Measurements
After successful calibration, the subject was asked to swallow to attempt equalization of the middle ear pressure to atmospheric pressure, then to refrain from swallowing after the insertion of the foam probe tip into the ear canal. The compressed foam ear tip with attached ER10C is then placed within the ear canal of the subject and allowed to expand for approximately 1 minute. Full expansion was marked by a feeling of blockage in the ear by the subject. As a leak-free seal is necessary for an accurate measurement, leaks were identified by (1) excessive noise in power reflectance at low frequencies; (2) an ear-canal impedance phase with an atypical pattern (typically, the impedance phase is negative and slowly increasing at low frequencies); and (3) increases in power reflectance at low frequencies with repeated measurements, which indicated the foam tip was still expanding. Wideband chirp responses from 200 to 6000 Hz were repeated until two sequential measurements varied by less than a few percent. Measurements are made in a quiet room.
2.3 RESULTS

2.3.1 Normal Subjects Power Reflectance

Power reflectance is the fraction of the forward pressure that is reflected back by the TM. A PR of 1 corresponds to the condition where all acoustic power is reflected back and reflectance of 0 corresponds to the condition where all power is absorbed at the TM. Power reflectances for the 58 normal ears show considerable variation. Figure 2.3A plots the PR from seven representative individuals (four right and three left ears) who were selected to represent the measurements obtained from the whole group of 58 ears. This plot demonstrates the variations in the frequency responses obtained. The seven examples include two ears with the most extreme reflectance measurements (plotted with gray lines) that illustrate the largest and smallest PR data recorded at frequencies less than 2 kHz and five ears that are generally range within one standard deviation of the mean (plotted in black). The overall shape of the measurements are similar, with PR near 1 at the low frequencies deceasing to a minimum somewhere between 1 and 3 kHz and then increasing, but substantial variations occur in the fine structure and minima and maxima of individual measurements. Figure 2.3B plots the mean and SD of PR. The mean PR is near 1.0 at the lowest measured frequencies (0.2–0.3 kHz), decreases to
a minimum between 0.3 and 0.4 from 1 to 4 kHz, and increases sharply at frequencies above 4 kHz.

![Graph showing power reflectance magnitudes and mean magnitudes.](image)

Figure 2.3: Magnitude of power reflectance PR (A) Seven representative ears selected to display the variety of frequency response curves that can be obtained. The two gray lines (subjects 6R and 23R) show the largest and smallest reflectance at frequencies below 2 kHz of all the normal ears measured. (B) Average and +/- 1 SD of PR for the 58 normal ears.

### 2.3.2 Test-Retest Reliability of Normal Power Reflectance

Both ears of seven subjects were tested repeatedly once a week for four weeks. Figure 2.4A, show the differences between the first measurement and the subsequent recordings of PR. The seven subjects included two subjects who were not considered “normal” by our strict criteria and were not included in Figure 2.3. Tympanometry on one of the two additional subjects showed a hypercompliant TM (gray dashed lines), and the second had a low-frequency air-bone gap due to a hypersensitive bone curve for 0.25 and 0.5 kHz although the air conduction thresholds were normal (gray dotted lines). These two subjects not included in the “normal hearing” category had some of the largest test-retest differences. The subject with the abnormally compliant TM (gray dotted lines) had large test-retest differences between 0.3 and 0.7 kHz, and the subject with the low-frequency air-bone gap (gray dashed lines) had large test-retest differences above 3 kHz. Figures 2.4B plots the mean and SDs of the test-retest differences in PR.
Figure 2.4: Reflectance measurements were made 1, 2, and 3 weeks after an initial measurement in both ears of seven subjects. (A) Power Reflectance differences for measurements at week 1, 2, and 3 with respect to the initial measurement. Grey and dashed measurements represent subjects who had normal audiograms did not meet the strict "normal" hearing criteria. (B) Mean (solid black) and SD (dashed) for the test retest measurements compared to the SD of the normal population from Figure 2.3 (thin solid).

2.3.3 Comparison to Published Data

Figure 2.5A compares our mean +/- 1 SD (thick black line with shaded area) with previously published means, while Figure 2.5B compares our median +/- 10-90% range (thick black line with shaded area) with previously published medians. Our data are generally similar to data recorded by other investigators. In the mid-frequency region (1–3 kHz), our data are very similar to Shahnaz and Shaw (2010) and Voss and Allen (1994), who both used the same measuring device (Mimosa) with similar calibration technique as ours. The data from the “young” population obtained by Feeney and Sanford (2004) are the most different from ours and show higher PR below 2 kHz. Table 2.1 shows the mean and/or range information for these comparisons.
Table 2.1: Comparative Studies

<table>
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<td>22 to 64</td>
</tr>
<tr>
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</tr>
<tr>
<td>Voss &amp; Allen 1994</td>
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<td></td>
<td>18 to 24</td>
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<td>Werner et al 2010</td>
<td>210</td>
<td></td>
<td>18 to 30</td>
</tr>
</tbody>
</table>

Figure 2.5: Comparisons with other published power reflectance measurements. (A) Comparison of the mean (black solid line) +/- 1 SD (shaded area) for the present study to the means (colored lines and symbols) and +1 or -1 SD (vertical error bars) of previously published data, including Voss and Allen (1994), Feeney and Sanford (2004), and Shahnaz and Shaw (2010). (B) Comparison of the median (black solid line) and 10% to 90% range (shaded area) for the present study to median and 10% to 90% of Shahnaz and Shaw (2010) and the 5% to 95% range of Werner et al. (2010).

2.3.4 Umbo Velocity Results

Figures 2.6 A &C show the magnitude and phase of the UV normalized by the ear-canal pressure, from the same seven representative individuals illustrated in above figures. These UV measurements are made in response to a nine-tone complex and therefore the data have a substantially coarser frequency resolution than the reflectance measurements, which are made in response to a broadband chirp.
Figures 2.6 B & D show the mean magnitude and phase of the $UV$ for this study is plotted in solid black line and the range of the mean +/- the SD is shaded gray.

The $UV$ data from this study were compared with a previous study from our laboratory (Whittemore et al. 2004), and these results are also plotted in Figure 2.6 B & D. The mean and SDs from the two studies are very similar, despite the fact that the criteria used to define “normal” differed slightly (as our criteria were more strict and required both ears to fit the criteria and required subjects to have normal tympanograms).

Figure 2.6: Magnitude and phase of normalized umbo velocity ($UV$) for (A&C) individual measurements from seven representative ears (same ears as in Fig 2.3) and (B&D) mean and standard deviation compared to previously published normal data from Whittemore et al (2004) (gray).
2.3.5  **Patients with Conductive Hearing Loss**

*Stapes Fixation*

Figures 2.7A &B show UV measurements from five representative ears that include the largest (P049L) and smallest (P056L) UV magnitudes (gray lines) among all 14 ears found to have stapes fixation. The gray shaded regions in Figure 1 show normative data of +/- 1 standard deviation (SD) around the mean. Overall, the UV magnitudes in ears with fixed stapes were lower than the normal-hearing average at low frequencies, and the UV phase tended to stay closer to 90 degrees at frequencies below 3 kHz when compared with normal. These results, indicative of a stiffer system, are similar to those previously published by our lab (Rosowski et al. 2008).

Power reflectance data for the same five representative patients are plotted in Figure 2.7C. The PR is generally higher than normal at low frequencies (400–1000 Hz), similarly indicative of a stiffer system. Overall, all of this data is consistent with a stiffer system. The one exception we found was in the case of ear P049L (the solid red line) that had a more compliant system than the normal mean. The two ears, (P049L, the most compliant) and (P056L, the most stiff) were consistently the two extreme outliers for all measurements. The most compliant ear (P049 L) had a tympanogram that was normal, and the stiffest ear (P056L) had a round-shaped tympanogram, consistent with a stiffer-than-normal system.
Figure 2.7: Comparisons of umbo velocity (UV) magnitude, UV phase, and power reflectance (PR) for 5 representative patients with stapes fixation: three typical examples (P008, P039, and P067) and two outliers (P048 and P056). The normal range +/- 1 SD from the mean is shown in gray. Panel (a) reveals a reduction in UV magnitude of up to nearly 2 SDs from the normal mean for frequencies below 1 kHz, with the exception of one case (P049). Panel (b) shows that UV phase remained near 90 degrees to higher frequencies compared to normal. Both magnitude and phase data are consistent with a stiffer system. Panel (c) shows an overall small increase in PR for frequencies below 1 kHz compared to the normal-hearing mean.

Ossicular Discontinuity

Figure 2.8 shows the results of the six ears that were confirmed to have a discontinuity of the ossicular chain. Four ears had complete (solid lines) and two had partial (dashed lines) ossicular discontinuity. Five of the six had normal
tympanograms while one ear (P054R) had an abnormally round-shaped tympanogram, which suggests a stiffer middle-ear system. Figures 2.8 A&B show plots of the UV magnitudes for all six ears with ossicular discontinuity. The gray lines to indicate the most extreme outliers. Five out of the six individuals showed an increase of UV magnitude of more than 2 SDs from normal mean at frequencies below 1 kHz, and UV phase that decreased abruptly around 400 to 800 Hz, similar to previous results (Rosowski et al. 2008). One ear (P054R, with a round-shaped tympanogram) had a low UV magnitude without an abrupt decrease in phase, consistent with a stiffened system. There was a tendency for UV magnitude to be higher and phase to change abruptly at lower frequencies for complete discontinuity when compared with partial discontinuity.

Power reflectance and absorbance measurements, shown in Figure 2.8 C, showed a notch in PR and a peak in absorbance level between 500 and 800 Hz in five of the six ears with discontinuity (Figs. 2.8 C&D). These results are similar to that published for one case by Feeney et al. (2003) and temporal bone studies by Feeney et al. (2009). These large notches in PR and peaks in absorbance level are consistent with a system that has had a reduction in damping. The one ear with the round-shaped (stiffer) did not follow this pattern, likely as the stiffness in the system was dominant for all measurement techniques.
OSSICULAR DISCONTINUITY

Figure 2.8: Comparisons of UV magnitude, UV phase, and PR for all 6 of the patients with ossicular discontinuity, two of which only had partial discontinuity (shown in dashed lines). P054 also had an abnormally round-shaped tympanogram, consistent with a middle-ear system stiffer than normal. The normal range +/- 1 SD from the mean is shown in gray. With the exception of P054, panel (a) reveals an increase in UV magnitude which can exceed more than 2 SDs from the normal mean below 1 kHz. Panel (b) shows a sharp decrease in UV phase compared to normal between 400 and 800 Hz. Panel (c) shows a notch in PR with a value greater than two SDs below the normal mean at frequencies between 500 and 800 Hz. These data are consistent with a reduction in damping and an increase in middle-ear compliance.

Superior Semicircular Canal Dehiscence

Figure 2.9 shows results from six representative ears with superior canal dehiscence (SCD), including the most extreme magnitudes of UV (P103R, P080R plotted with gray lines) and PR (P074L, P082L). All of these ears had normal
tympanograms. The outliers for PR are not the same as the outliers in UV in the case of SCD. Most measurements of UV had a magnitude larger than the mean and a phase somewhat smaller than the mean at frequencies near 1 kHz, similar to previous data (Rosowski et al. 2008). The PR measurements showed a notch with a value about 2 SDs below the normal mean at frequencies near 1000 Hz.

SUPERIOR SEMICIRCULAR CANAL DEHISCENCE

Figure 2.9: Comparisons of UV magnitude, UV phase, and PR for 6 representative patients with superior canal dehiscence: two typical examples (P052 and P087), the two outliers for UV magnitude (P080 and P103) and the two outliers for PR (P074 and P082). The normal range +/- 1 SD from the mean is shown in gray. Panel (a) reveals a slight increase in UV magnitude from the normal mean near and below 1 kHz. Panel (b) shows a slight decrease in UV phase compared to normal in this same frequency range. Panel (c) shows a notch in PR measurements with a value about two SDs below the normal mean at frequencies near 1000 Hz.
2.4 DISCUSSION

Reflectance measurements have great potential for clinical utility. In a truly “one-dimensional” tube system of constant cross section, rigid (lossless) walls, and a lossless sound conducting media, the pressure reflectance depends on the combination of the terminating impedance and the canal cross-section, and the magnitude of the reflectance \(|R|\) is independent of the distance between the measurement location within the tube and the terminating “reflecting” surface. The \(PR\), the square of the pressure reflectance magnitude \((PR)\), similarly depends on the tube’s cross-section and termination, and is also independent of the position in the tube. The independence of position in the ear-canal is an attractive quality of a clinical test, as variations in this position are clinical reality. In addition, reflectance measurements are easy to make with an already FDA approved device and are of relatively low cost, especially when compared to UV measurements, which require a highly trained individual to aim the laser, an additional individual to run the computer, and expensive equipment. Thus, there is a great motivation for gaining a better understanding of how reflectance behaves in both normal and patient populations in order to determine how we may be able to use these measurements for diagnostic purposes.

2.4.1 Normal Measurements

The reflectance measurements in our normal population are consistent with a high \(PR\) at frequencies below 0.5 kHz as well as at frequencies above 5 kHz. Between these limits is a range of relatively low-reflectance region that corresponds roughly with the frequency range of lowest hearing threshold under earphones (Allen et al. 2005). Although these general trends are apparent in the individual measurements, there is also significant variability in reflectance between different ears.

Substantial variations in the normal population were observed, and there are several potential sources of this variability. One source of variability in our measurements is the intrasubject variation we observed between tests and retests.
of PR in a small population (Fig. 2.4). The +/- 0.1 variations we see in repeated measurements of PR made over a 4-wk interval accounts for a significant fraction of the +/- 0.15 SD observed in the normal population. This test-retest performance is similar to that of Werner et al. (2010). These test-retest differences could be caused by small differences in the placement of the probe and ear tip within the external ear-canal, as the cross-sectional area of the ear-canal changes along the length of the canal. We calculate the reflectance in adults based on the size of the ear-tip used, and small differences between the actual canal cross-section and the cross-section used in the measurements are known to cause small but consistent deviations in the computed PR (Keefe et al. 1993, 1994; Huang et al. 2000a). It is also possible that small differences in middle ear pressure between measurements can affect reflectance (Margolis et al. 1999) just as they affect the measured middle ear impedance during tympanometry. We attempted to control for such variations by having the subjects swallow several times before our measurements, but the effectiveness of such procedures is variable. These sources of variability can also account for intersubject differences, along with individual differences in impedance at the tympanic membrane, which can result from differences in the TM, ossicles, and cochlear and middle-ear cavity impedance between subjects (Zwislocki & Feldman 1970; Margolis & Shanks 1985; Stepp and Voss 2006; Voss et al. 2008).

Variability could also result from differences in age, gender, and ear side (Shahnaz and Bork 2006; Feeney and Sanford 2004; Werner et al. 2010). We found small but significant gender-related differences in PR. The PR measured in females tends to be higher than that in males at frequencies of 2 kHz and below and lower than males at frequencies of 3 to 6 kHz. However, only the difference at 4 kHz was significant at the $p <0.05$ level. We found no age related differences present in our study, although the ages of our subjects were of a relatively small range. The differences in reflectance between the left and right ear approached 15% of the grouped mean at 2 and 8 kHz but were only significantly different from zero ($p$ value<0.05) at 0.3 kHz. As the results showed, the umbo velocities measured in this study (n=58) were similar to the umbo velocities measured in our previous study (n=56) (Whittemore
et al., 2004) for subjects with normal hearing (Fig. 2.7).

2.4.2 Patients with Conductive Hearing Loss

We made pre-diagnostic measurements of UV and PR in 31 patients with conductive hearing loss who were ultimately diagnosed as having either stapes fixation, ossicular discontinuity, or superior canal dehiscence as the cause of their CHL. These three pathologies are representative of the majority of cases of conductive hearing losses seen in patients who have a healthy TM and an aerated middle ear on otoscopic examination.

Figures 2.7, 2.8, and 2.9 compared our measurements on ears with conductive hearing loss to the normal data. These comparisons demonstrate how the frequency responses of mechanical measurements differ. For stapes fixation, we generally see increases in PR and decreases in absorbance and UV magnitude measurements at low frequencies when compared to normal, as well as UV phases that tend to stay close to 90 degrees up to higher frequencies than normal. All of these results are consistent with a stiffer system. For ossicular discontinuity, we see sharp decreases in the form of a notch below 1 kHz in the PR, with a corresponding peak in the UV and absorbance in similar frequency ranges. The UV phase also exhibits a phase transition in this frequency range. Collectively these results are consistent with a system exhibiting a resonance due to a potential decrease in damping at the TM as well as an increase in compliance. Some differences were observed between the patients with partial and complete disarticulation, as there was a tendency for UV magnitude to be higher and phase to change abruptly at lower frequencies for complete discontinuity when compared with partial discontinuity. Finally, patients with SCD showed similar patterns as patients with ossicular discontinuity, but with smaller alterations in magnitude. There is a slight increase in UV below 1 kHz, while there is a notching pattern (within a slightly higher frequency range than for discontinuity) in the PR. This is also consistent with a system exhibiting a resonance due to a decrease in damping at the TM, without the affect of an increase in compliance that we see in the disarticulated case (resulting in a notch at a higher
frequency than in the disarticulated case) due to the fact that the annular ligament is still present.

2.5 CONCLUSIONS

Umbo velocity measurements have been made and studied in our laboratory for over 10 years and have been shown to aid in the diagnosis of various middle and inner ear pathologies in our institution (Rosowski et al., 2003, 2008; Merchant 2007a, b) and there is no question that an objective noninvasive diagnostic method such as $UV$ measurements before surgery contributes to the understanding of pathology before surgery. These improvements in presurgical diagnosis lead to improved presurgical preparation, better counseling of patients as to surgical risks and benefits, and the prevention of unnecessary surgeries. Unfortunately, there are practical issues with umbo velocity measurements including high cost, a technique which requires two professionals to make measurements—a trained clinician to operate the microscope-laser device and aim the laser on the umbo and a trained computer operator to gather and evaluate the data, the lack of FDA approval, and the dependence of the measurements on the presence of a naturally reflective bright spot on the TM, the light reflex, which is not present in all patients due to normal anatomical differences. Thus, the need for a practical presurgical diagnostic for widespread clinical use still exists. Power reflectance measurements have shown promise as a presurgical differential diagnostic of conductive hearing loss, and this chapter systematically explored $PR$, as well as $UV$ measurements, in a strict normal population and compared these measurements to measurements made in patients with conductive hearing loss that was determined to be caused by either stapes fixation, ossicular discontinuity, or superior semicircular canal dehiscence. The frequency dependence of the $PR$ measurements was different for the three pathologies: stapes fixation resulted in small increase from normal at low-to-mid frequencies, while large narrowband decreases from normal were seen for ossicular discontinuity (between 500 and 800 Hz) and SCD (<1 kHz). Chapter 2 will explore how we can use these measurements for diagnostic purposes.
2.6 REFERENCES


Keefe, D., Bulen, J., Campbell, S., et al. (1994). Pressure transfer function and absorption cross-section from the diffuse field to the human infant ear canal. *J


Chapter 3

Using Reflectance as a Diagnostic Tool

3.1 Differential Diagnosis of Conductive Hearing Loss using Reflectance

This section of this chapter is based on a publication that describes measurements of reflectance in patients. The first part describes our efforts to use reflectance and umbo velocity to differentiate among ossicular pathologies that were independently confirmed in a patient population (Nakajima et al. 2012). As a co-author in this report I was responsible for much of the data gathering and the analysis of the data. Although, I did not conceive this studies, I was involved in all aspects of the work.

3.1.1 INTRODUCTION

The causes of conductive hearing loss are often difficult to determine accurately despite the frequent occurrence of various middle-ear diseases in the clinic (Merchant et al 1998). Current clinical practice rarely utilizes assessment of middle-ear mobility to aid in the diagnosis of middle-ear disease, with the exception of tympanometry, which is usually measured at only one frequency. Current work suggests that various other measurements of middle-ear mobility may aid in the differential diagnosis of middle-ear disease, particularly measurements that consider wide frequency ranges (Rosowski et al 2008, Feeney et al 2003, Allen et al 2005, Shahnaz 2009).

In patients with conductive hearing loss, the loss is most commonly due to fixation of the stapes, ossicular discontinuity, or a third window lesion of the inner ear such as superior semicircular canal dehiscence (SCD) (Merchant and Rosowski, 2010). Currently, there are no diagnostic tests that can reliably differentiate between the pathologic conditions responsible for conductive hearing loss. The size and frequency dependence of the air-bone gap on standard audiometry show large variations within and among these disorders, so that the audiogram alone cannot
provide a differential diagnosis (Rappaport and Provencal 2002). Additionally, stapes fixation, partial discontinuity, and SCD cannot be reliably distinguished by tympanometry (Harford 1980, Fowler and Shanks 2002). A computed tomographic (CT) scan is of diagnostic value for third window lesions such as SCD, but its resolution at present is not sufficient to permit reliable diagnosis of ossicular pathology (Chakers and Augustyn 2003). High-resolution CT is also relatively expensive and involves exposure of patients to radiation; hence, it is not practical to subject every patient with conductive hearing loss to a CT scan. Presence or absence of acoustic reflex can be helpful in distinguishing ossicular disorders from third-window lesions (Minor 2005), but it does not help differentiate between ossicular fixation and discontinuity, and in some cases is not present in cases of third window pathologies (Mukerji et al. 2010), thus a third-window lesion can be missed. Vestibular evoked myogenic potential (VEMP) testing is helpful in diagnosing SCD (Minor 2005) but cannot differentiate or diagnose ossicular pathologies; moreover, VEMP testing is not widely available.

A diagnostic test that differentiates among these disorders and that can be used in an office setting would be of clinical value. Patients with a third window lesion would be spared unnecessary surgical exploration of the middle ear and presurgical knowledge of the type of ossicular pathology likely to be encountered at surgery (e.g., stapes fixation versus ossicular discontinuity) would help an otologist in preoperative counseling of patients regarding surgical risks and in preoperative planning. Chapter 2 explored how these measurements in patients with conductive hearing loss compare to our measured normal population. However, patients can be readily separated into those with normal hearing and those with conductive hearing loss by standard audiometry. The task that is difficult for otologists is to differentiate among etiologies responsible for conductive hearing loss that have a normal-appearing TM and an aerated middle ear. Thus, this chapter focuses on developing diagnostic algorithms using tools such as umbo velocity, UV, and power reflectance, PR, to differentiate between various pathologies responsible for conductive hearing loss.
As explained in Chapter 2, umbo velocity measurements have been shown to contribute to the non-invasive diagnosis of middle-ear disorders, but this technique is not FDA approved for clinical use, is expensive, and requires a skilled clinician to operate the device. The reflectance measurement system is FDA approved, less expensive, and simpler to operate; however, it is yet to be determined if this device can differentially diagnose various middle-ear pathologies. Comparisons of umbo velocity and reflectance in the same ear can aid in determining the ability to diagnose the etiology of conductive hearing loss in ears with a normal tympanic membrane and an aerated middle ear. This study explored how the measurements made as a part of Chapter 2 can be used to differentially diagnose conductive hearing loss. We determine the clinical utility of reflectance as a differential diagnostic and compare the diagnostic accuracy of UV measurements (which we have been using for many years) and measurements of PR in the same patients.

3.1.2 METHODS
The methods for this study are explained in great detail in Chapter 2. Briefly, UV and PR measurements were made on 104 ears and analyses were completed on 31 with subsequent confirmation of stapes fixation, ossicular discontinuity, or SCD. Pure-tone audiometry (on all 31) and tympanometry (on 28 out of 31) was also measured. Confirmation of pathology consisted of:

Stapes Fixation: diagnosis confirmed at subsequent surgery and post-stapedectomy air-bone gap was less than 10 dB to ensure no confounding pathology contributed to the hearing loss (n=14).

Ossicular Discontinuity: diagnosis confirmed at subsequent surgery (n=6).

SCD: diagnosis confirmed if high-resolution CT scan showed a dehiscence and VEMP thresholds were abnormally sensitive (Minor 2005) (n=11).
Laser Doppler Vibrometry was used to measure $UV$. A laser beam was focused on the light reflex near the umbo of the tympanic membrane and a simultaneous 9-tone stimulus was played into the ear canal. The resulting velocities of the umbo were analyzed as the ratio of the measured velocity to the measured sound pressure in the ear canal near the tympanic membrane. See Figure 2.1 and Chapter 2 for more details.

Reflectance ($R$) is the complex ratio between the reflected pressure wave and the forward pressure wave. The most common permutations of $R$ that are considered in this work are power reflectance ($PR=R^2$), which has a value between 0 (all energy absorbed) and 1 (all energy reflected), and absorbance level [$10\log(1-PR)$], which allows for logarithmic analyses of reflectance measurements. Reflectance measurements are collected using the Mimosa system by inserting a foam tip into the ear canal, which then expands to create a seal. This tip is attached to a microphone and sound source that applies a wideband chirp stimulus from 200 to 6000 Hz. For each patient, two sequential chirp measurements were collected and averaged. See Figure 2.2 and Chapter 2 for more details.

3.1.3 RESULTS AND DISCUSSION

3.1.3.1 Comparison of Reflectance and Umbo Velocity Measurements Between Pathologies

Figure 3.1 compares mean $\pm$ 1 or -1 SD (shown by error bars) $UV$ (A) and $PR$ (B) between stapes fixation (red), ossicular discontinuity (green) and superior semicircular canal dehiscence (blue), directly comparing results from Figures 2.7 to 2.9. Small decreases in $UV$ and increases in $PR$ are seen for stapes fixation at low-to-mid frequencies (400-1000 Hz) when compared to normal. Narrowband increases in $UV$ and decreases in $PR$ are seen for ossicular discontinuity and superior canal dehiscence. These changes appear in the lower frequencies (500-800 Hz) for discontinuity, and at mid-frequencies (~1000 Hz) for SCD.
In general, the differences in \( UV \) and \( PR \) that we observe between normal and SCD ears are reduced versions of the differences observed between normals and ears with ossicular interruption. Smaller changes in \( UV \) magnitude, \( UV \) angle, and \( PR \) are seen for SCD, with the changes in SCD occurring at higher frequencies as compared with ossicular discontinuity. This provides separation between SCD and ossicular discontinuity effects. In addition, the changes resulting from stapes fixation occur in the opposite direction of changes resulting from ossicular discontinuity and SCD when compared to normal, potentially providing some separation of all three pathologies within certain frequency ranges. That said, there still exists substantial overlap between individual pathologies, such that neither \( UV \) nor \( PR \) alone could serve as a highly sensitive and specific stand-alone diagnostic tool to separate out the three pathologies responsible for conductive hearing loss.

**MEAN DATA**

Figure 3.1: Comparisons of mean \( UV \) magnitudes (in panel a) and \( PR \) (in panel b) for stapes fixation (n=14, red), ossicular discontinuity (n=6, green), and superior canal dehiscence (n=11, blue).

**3.1.3.2 Audiometric Comparisons**

Figure 3.2 displays the mean air-bone gap +1 or -1 SD (shown by error bars) for stapes fixation (red), ossicular discontinuity (green) and superior semicircular canal
dehiscence (blue). Audiometry separates out conductive hearing loss from normal for all three pathologies quite well, as shown simply by the presence of an air-bone gap. The clinical challenge that we are trying to solve, however, is to determine which pathology is the cause of the conductive hearing loss.

While there is substantial overlap in the air-bone gap, there is more separation between the three pathologies in the 1 to 4 kHz range than in other frequency ranges (as shown in Figure 3.2). The mean of the air-bone gaps for stapes fixation (red) showed large conductive losses (40–60 dB) at low frequencies and smaller losses at high frequencies (~20 dB). The mean air-bone gap for ossicular discontinuity resulted in large air-bone gaps (40 – 60 dB) at low frequencies, similar to air-bone gaps observed with stapes fixation. At higher frequencies, however, the air-bone gap for ossicular discontinuity was larger than for stapes fixation. For the two patients with partial discontinuity, the average air-bone gap across the frequency range of 250 to 4000 Hz was between 17 and 20 dB. For the four patients with complete discontinuity, the average air-bone gap across the frequency range of 250 to 4000 Hz was higher, ranging from 40 to 59 dB. This data may suggest that the air-bone gap is dependent on the degree of discontinuity. The air-bone gaps experienced by SCD patients (blue) were more pronounced at low frequencies than at high frequencies and were around 20 dB smaller when compared with the gaps produced by fixation or interruption at the same frequency.

Thus, while neither UV, PR, nor ABG information alone can serve as a highly sensitive and specific stand-alone diagnostic tool, combining air-bone gap information with UV or PR data may provide a better differentiation between pathologies.
Figure 3.2: Comparison of mean air-bone gaps +/- 1 SD for the three pathologies. Results are plotted from 14 ears with stapes fixation (red), 6 ears with ossicular discontinuity (green), and 11 ears with superior canal dehiscence (blue).

3.1.3.3 Comparison of Reflectance and Umbo Velocity with ABG for Differential Diagnoses

Our data shows large overlaps in the size and frequency dependence of air-bone gaps within and between the three pathologies, so that audiometry by itself did not permit accurate preoperative diagnosis of the etiology for the conductive loss. Tympanometry was also not sensitive in diagnosing the ears studied: 10 of 11 ears with fixed stapes, 5 of 6 with ossicular discontinuity, and all 11 ears with SCD had normal tympanograms. Our UV and PR measurements show a clearly distinctive pattern for ossicular discontinuity, however, there was sufficient overlap between the fixed stapes and SCD cases such that neither UV nor PR alone could serve as a highly sensitive and specific stand-alone diagnostic.

Our lab has shown in the past that UV measurements combined with audiometric data can differentiate various pathologies that cause conductive hearing loss (Rosowski et al. 2008). We performed a similar analysis for the dataset in the present study for both UV and absorbance level [10log(1-PR)], which is directly related to PR but serves as a better comparison to UV than PR as it reflects what is being absorbed by the ear and not the portion reflected and is also on a dB scale.
Figure 3.3 shows plots of UV (A) or absorbance level (B) versus the air-bone gap for all 31 ears. In Figure 3.3A, for each ear, UV magnitudes measured for the ears with conductive hearing loss normalized to the UV magnitudes of normal-hearing mean (averaged over 300–700 Hz) were plotted against the air-bone gap (averaged over 1–4 kHz). In Figure 3.3B, a similar figure was made for absorbance level measurements where each ear was referenced to the mean of the absorbance level measured in normal-hearing subjects, which was averaged over 0.6 to 1 kHz, and plotted against the air-bone gap (averaged over 1–4 kHz). We chose these ranges based on where the largest differences were observed in the data between pathologies.

Exclusive boundaries were easily drawn around most, if not all, of the members of each pathological group, with stapes fixation in red, ossicular discontinuity in green, and SCD in blue. It can be appreciated from the boundaries drawn that in both UV and PR, most of the pathologies separate out quite well. For UV results, 29 of the 31 ears were easily separated into the three pathological groups. Exceptions included one ear with a fixed stapes that fell into the ossicular discontinuity area and one ossicular discontinuity in the stapes fixation area. For absorbance results, 28 of the 31 ears were separated into the three pathological groups. There were three exceptions: one stapes fixation fell into the area bounded by ossicular discontinuity, one ossicular discontinuity fell between the SCD and stapes fixation area, and one stapes fixation fell on the border of the SCD area. The fixed stapes ear that was in the ossicular discontinuity area for both the UV and absorbance level scatter plots was ear (P049L), which had UV and absorbance level measurements consistent with a compliant middle ear, possibly caused by a confounding factor such as a hypermobile tympanic membrane. The ossicular discontinuity case, found at the lower-left corner of the stapes fixation area in the UV scatter plot and between the SCD and stapes fixation area in the absorbance level scatter plot (Fig. 6B), was ear (P054R), which had the tympanogram, UV, and absorbance level measurements consistent with a stiffer system, again possibly caused by a confounding pathology existing in the system somewhere, perhaps an abnormally stiff tympanic membrane.
Figure 3.3: Panel (a) shows UV magnitudes referenced to the normal-hearing mean (averaged over 300-700 Hz) plotted against the air-bone gap (averaged over 1-4 kHz). The different symbols and colors represent each of the three pathologies. All three disorders were separable from each other for 29/31 ears. Panel (b) shows absorbance level measurements where each ear was referenced to the normal-hearing mean (averaged over 0.6-1 kHz), and plotted against the air-bone gap (averaged over 1-4 kHz). Using absorbance level in combination with the air-bone gap also allowed separation of the 3 pathologies for 28/31 ears. The sensitivity and specificity of these diagnostic techniques is shown in the table below.
The analysis illustrates that both UV or absorbance level, in conjunction with audiometric data, were able to separate correctly nearly all of the ears into the three different pathologies. The computed sensitivity and specificity based on the combined audiometric and UV or absorbance data are listed in Table 3.1. Overall, for both types of diagnostic measurements, the range of sensitivity was 83% to 100% and specificity 94% to 100%. In the case of stapes fixation, umbo velocity had slightly higher sensitivity but lower specificity than absorbance level. For ossicular discontinuity, umbo velocity and absorbance level had the same sensitivity and specificity. For SCD, umbo velocity had the same sensitivity but slightly higher specificity than absorbance level.

Table 3.1: Sensitivity and Specificity of Umbo Velocity and Absorbance Level Measurements

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbo Velocity with Air-Bone Gap Measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stapes Fixation</td>
<td>93%</td>
<td>94%</td>
</tr>
<tr>
<td>Ossicular Discontinuity</td>
<td>83%</td>
<td>96%</td>
</tr>
<tr>
<td>SCD</td>
<td>100%</td>
<td>100%</td>
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<tr>
<th>Absorbance Level with Air-Bone Gap Measurements</th>
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<tr>
<td>Pathology</td>
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<td>Specificity</td>
</tr>
<tr>
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<td>86%</td>
<td>100%</td>
</tr>
<tr>
<td>Ossicular Discontinuity</td>
<td>83%</td>
<td>96%</td>
</tr>
<tr>
<td>SCD</td>
<td>100%</td>
<td>95%</td>
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</table>

3.1.4 CONCLUSIONS

This study demonstrates that PR measurements can aid in the differential diagnosis of pathologies causing conductive hearing loss preoperatively. Our results show that the frequency dependence of the PR measurements was different for the three pathologies, and that PR measurements combined with audiometry showed high sensitivity and specificity as a clinical diagnostic tool in the differential diagnosis of these disorders.
3.1.5 REFERENCES


3.2 Power Reflectance as a Screening Tool for the Diagnosis of Superior Semicircular Canal Dehiscence

While the differential diagnoses of the pathology causing a CHL, including SCD, is of great interest, the diagnosis of SCD in patients who do not have a CHL is another clinical challenge. Given the distinctive notch pattern observed in the PR frequency responses from Chapter 2 and 3.1, we were motivated to explore if PR could serve as a diagnostic screener for any patient thought to possibly have SCD. This work describes a technique capable of identifying SCD in a group of patients with good sensitivity and selectivity. The following work summarizes a manuscript that is currently in press: Merchant, G.R., Roosli, C., Niesten, M.F., Hamade, M.A., Lee, D.J., McKinnon, M.L., Ulku, C.H., Roswoski, J.J., Merchant, S.N., Nakajima, H.H. (2013). Power Reflectance as a Screening Tool for the Diagnosis of Superior Semicircular Canal Dehiscence. Otol Neurotol, in press. My role in this work as one of the principal authors was to gather the data, analyzes it, refine the differential diagnostic scheme and write the paper. Only minor modifications of the in-press manuscript have been made for formatting the work into this dissertation.

3.2.1 INTRODUCTION

Superior canal dehiscence (SCD) is considered rare, but since its initial description by Minor in 1998 (1), identification of patients with SCD syndrome (SCDS) continues to increase with awareness of this condition and improvements in diagnostic methods. The clinical diagnosis of SCDS is generally suspected in the subset of patients with signs and symptoms of: a) a vestibular nature such as dizziness and vertigo induced by noise (Tullio’s) or pressure (Hennebert’s), and/or b) an auditory nature such as low-frequency conductive hearing loss with normal tympanometry and stapedial reflexes and supranormal bone conduction on pure tone audiometry as reflected by hypersensitivity to bone-conducted sounds (e.g., hearing eye movements or footfalls). However, patients with SCDS may present with other common symptoms that mimic a number of diseases frequently encountered by otolaryngologists. These symptoms include non-specific intermittent dizziness, unsteadiness, aural fullness, or autophony (2). Wrong diagnoses have resulted in the delay of proper treatment, consultation of multiple specialists, and unnecessary surgery. These diagnoses include: psychiatric disease, migraine, Ménière’s disease, Eustachian tube dysfunction (leading to tympanostomy
Various tests are used today to help confirm the diagnosis of SCD in patients who have radiologic imaging evidence of a bony defect, including cervical vestibular evoked myogenic potential (cVEMP) (3). Zuniga et al. (4) reported high sensitivity and specificity for cVEMP to diagnose SCD. However, cVEMP presently falls short due to: a) lack of standardization, b) lack of appropriate signal processing schemes (to account for differences in background muscle activity, muscle mass, and fatigue), c) lack of artifact rejection schemes for detection in noise, and d) inconsistencies across institutions and subjects (5). Although cVEMP testing has not yet received FDA approval, many institutions perform cVEMP in the workup of a patient in whom SCDS is suspected. Ocular vestibular evoked myogenic potential (oVEMP) has been recently shown to be useful for diagnosing SCDS (4); however, few institutions perform this test. In the context of conductive hearing loss, stapedial reflex testing is useful, as the reflex is often present in SCDS and absent in other conductive pathologies (2). Nevertheless, the stapedial reflex may be absent in SCD ears due to other factors. Another characteristic in SCDS patients is hypersensitive low-frequency bone conduction (2, 6), but the prevalence of this marker is not well known. From the series of patients used in Niesten et al. (7), we find that 57% (73/129 ears) have bone conduction thresholds better than 0 dB at one or more frequencies (unpublished data).

The reference for the diagnosis of anatomic SCD is high-resolution computed tomography (CT). However, if only common non-specific vestibular or auditory symptoms are present, SCDS is not suspected during the initial workup, and a high-resolution temporal bone CT scan is not performed. A simple, inexpensive non-invasive SCD diagnostic screening test that would aid a general otolaryngologist in the initial consultation would be of value to determine if further testing (CT and VEMP) should be performed. Additionally, very small dehiscences (<0.5 mm diameters) that cannot be detected by CT might result in significant symptoms [e.g.,
small dehiscences have been shown to sometimes produce larger changes in mid-frequency intracochlear pressure than large dehiscences (8). Consistent with this finding, patients with thin bone over the superior semicircular canal with SCDS had reduced symptoms by surgical plugging (9). Furthermore, the bony wall of the semicircular canal can be uneven and 'scalloped' (10). This structure may result in multiple micro-openings when the bone is thinned, leading to similar effects like very small dehiscences (8).

In the past we have demonstrated that in cases of conductive hearing loss, non-invasive measurements of sound-induced umbo velocity using laser-Doppler vibrometry or power reflectance (PR) can reliably differentiate between SCD and other conductive lesions (11, 12). Reflectance (R) is the complex ratio between the reflected pressure wave and the forward pressure wave propagating in the ear canal. Power reflectance is calculated as the square of the magnitude of the reflectance, \( PR = |R|^2 \), where \( PR \) generally ranges between 0 and 1 (where 1 indicates all energy is reflected and 0 indicates all energy is absorbed).

In this study we determine if \( PR \) measurements (an inexpensive FDA-approved test that is easily performed), coupled with a new detection algorithm sensitive to specific SCD features, can act as a simple non-invasive SCD screening test for patients with varying symptoms (vestibular and/or hearing related). Such a screening test could be helpful at primary centers to provide an indication of SCD with high sensitivity and reasonable specificity, helping to determine whether more expensive or invasive diagnostic procedures are warranted.

3.2.2 MATERIALS AND METHODS
This work was approved by the institutional review board of the Massachusetts Eye and Ear Infirmary (MEEI). We recruited 50 patients with 59 ears that were diagnosed with SCD by high-resolution CT. We utilized specialized methods in conjunction with CT measurements for determining the size of the dehiscence as
described below and in more detail in Niesten et al. (7). A total of 32 patients (17 females and 15 males) met the following inclusion criteria: a) presence of SCD on CT scan, b) absence of any middle ear disease such as cholesteatomas or tympanic membrane (TM) lesions, and c) absence of previous ear surgery except for placement of tympanostomy tubes more than two years before measurement. The mean age was 48.1 years, ranging from 25 to 69 years old. Eight patients had bilateral SCD, resulting in the inclusion of a total of 40 ears with SCD. Of these 40 ears, 27 were on the left side, and 13 on the right side. They were referred for PR measurements from the Otologic Clinic at the Massachusetts Eye and Ear Infirmary between January 2010 and July 2012.

All patients included in this study reported at least one sign or symptom such as autophony, fullness of the ear, hyperacousis (including the sensation of hearing one’s eye motion, pulse or footsteps), tinnitus, hearing loss, and/or various forms of dizziness or unsteadiness. The TM appeared normal on microscopic observation in all patients. Patients underwent audiometric air conduction and bone conduction threshold testing, and most underwent stapedial reflex testing, tympanometry, and cVEMP testing. A summary of all of the testing results in our population can be found in Table 3.2.

Table 3.2: Summary of audiologic data. CHL is conductive hearing loss.

<table>
<thead>
<tr>
<th>Summary of Audiologic Data</th>
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<tbody>
<tr>
<td>Test Procedure/Condition</td>
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<tr>
<td>Conductive Hearing Loss</td>
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<tr>
<td>Hypersensitive Low-Freq Bone Conduction</td>
</tr>
<tr>
<td>Acoustic Reflex w/CHL</td>
</tr>
<tr>
<td>Acoustic Reflex w/o CHL</td>
</tr>
<tr>
<td>Normal Tympanometry</td>
</tr>
<tr>
<td>cVEMP Suggestive of SCD</td>
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Table 3.3: Details of audiologic data. CHL is conductive hearing loss.

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<th>Vestibular Symptoms</th>
<th>CHL/ABG</th>
<th>VEMP</th>
<th>Acoustic Reflex</th>
<th>Tymp</th>
<th>Hypersensitive Bone Conduction</th>
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All audiologic testing was performed by audiologists at the Massachusetts Eye and Ear Infirmary using standard techniques (12, 13). Conductive hearing loss was defined as mean air-bone gap (ABG) between 250 and 1000 Hz of 10 dB or more. Seventeen out of the 40 SCD ears (42.5%) fulfilled this criterion. Bone conduction thresholds were evaluated at levels as low as -10 dB HL in all patients, and hypersensitive bone conduction (less than 0 dB HL at one or more frequencies) was
noted in 19/40 patients with SCD. Acoustic reflex was performed in 16/17 ears with conductive hearing loss and was present (reflex elicited for <95 dB HL) in 14/16 (87.5%) ears. Reflex testing was performed in 13/23 ears without conductive hearing loss and found present in 11/13 (84.6%). Thirty-seven ears underwent 226 Hz tympanometry with normal results in 35/37 ears (2 had sharp peaks consistent with increased mobility).

Because of variability across institutions, we included in our analysis only the 33/40 SCD ears with cVEMP tests performed at the MEEI. The cVEMP thresholds at 250, 500, and 1000 Hz were compared to the 95% confidence interval of established thresholds for normal subjects (14). If two or more of the three frequencies had thresholds below the normal confidence limits (peak sound pressure of 105 dB at 250 Hz, 95 dB at 500 Hz, 100 dB at 1000 Hz), the test was considered suggestive of SCDS (14). Sixteen of the 33 tested ears (48.5%) showed measurements consistent with SCDS.

In the 38 patients with high-resolution CT scans performed at MEEI, the length of the SCD was determined using the analysis methods described in Niesten et al. (7). High-density temporal bone CTs were analyzed by viewing the oblique multiplanar reformatted images while making a curved planar reconstruction of the superior semicircular canal. From the reconstruction, 0.2 mm thick radial sections were analyzed for radiodensity of the bone overlying the superior semicircular canal. An optical density of <300 Hounsfield Units was defined as absence of bone. PR was measured with an FDA-approved commercially-available Mimosa Acoustic HearID system (Champaign, IL USA). Power reflectance measurements used wideband (0.2-6 kHz) chirp stimuli of 60 dB SPL intensity and three-second duration with individually calibrated acoustic systems as previously described (12, 13).
3.2.3 RESULTS

3.2.3.1 Power Reflectance (PR)

Three representative PR measurements from ears with SCD are plotted in Fig. 3.4 A, along with +/- one standard deviation around the mean (gray region) determined from 58 normal ears (13). Most of the measurements from SCD ears had a prominent notch-like local minimum centered between 0.6 and 1.8 kHz that was more than 1.5 standard deviations below the normal mean, followed by a local maximum at a higher frequency. Figure 1B plots the mean (solid black line) of 40 SCD ears and +/- one standard deviation (dashed lines). The normal ears are plotted as +/- 1 standard deviation (gray region) around the mean (gray line). Averaging across ears smoothes out the notches that occur at different frequencies in the different SCD ears, but the SCD mean near 1 kHz is still about one standard deviation lower than normal mean.

Figure 3.4: (A) Three representative examples of PR recorded from ears with SCD. The gray shaded region represents one standard deviation around the mean of 58 normal ears. Most ears with SCD have a distinctive notch near 1 kHz. (B) PR mean (black solid line) and one standard deviation around the mean (dashed line) for ears with SCD (n=27). PR mean (gray solid line) and one standard deviation around the mean (gray shading) for normal ears.
3.2.3.2 Notch Detection Algorithm for PR Measurement to Diagnose SCD

As shown in Fig. 3.4A, ears with SCD generally exhibited a notch near 1 kHz in the PR curves. To determine if this feature in the PR can be used as a diagnostic indicator for SCD, we developed a ‘notch-detection’ algorithm (implemented in MATLAB) to identify their occurrence in individual measurements. The simple notch-detection algorithm relies on three parameters that allow for variations in the notch shape and frequency range. Details of the algorithm are described in the appendix available in section 3.2.6. Figure 3.5 is a representative PR difference curve (the difference between a PR response from an individual with SCD and the mean PR of normal ears). Three parameters can be adjusted in the algorithm: notch frequency range, minimum notch depth, and minimum notch size. This algorithm determines the presence of a V-shaped notch, within the parameters that determine the range of shape and size, in a particular frequency range. Figure 3.5 shows an example where the algorithm has sensed the existence of a notch.

Figure 3.5: The difference in PR between an example SCD and normal mean.
We were able to adjust the three parameters in the algorithm (notch frequency range, minimum notch depth, minimum notch size) to distinguish between SCD and normal ears with high sensitivity and moderately high specificity. Detection thresholds of the above parameters were originally determined based on optimization around a subset of the data (26/40 ears) together with the normal population of 58 ears. Details of how we determined optimized parameters are described in the appendix of this chapter. Later, the same method of determining the best parameter values were repeated for the 40 SCD ears with respect to the 58 normal ears, resulting in the same optimized parameter set, which demonstrated the validity of the selected parameter values. Fig. 3.6 A & B show receiver-operating characteristic (ROC) curves calculated for the 40 SCD ears and 58 normal ears for parameter variations. In Figure 3.6 A, we compare the use of notch size as a decision variable after first applying two different minimum notch depths. In Figure 3.6 B we look at the use of notch depth as a decision variable after first applying a minimum notch size. A minimum notch size on the order 0.1 and a minimum notch depth between 0.05 and 0.1 were found to separate most SCD ears from normals.
After defining useful parameters, the performance of the diagnostic screening test was quantified. The algorithm was used on separate individual PR measurements (40 SCD and 58 normal ears). Optimal sensitivity occurred with a notch frequency range of 585-1876 Hz, a minimum notch size of 0.097, and a minimum notch depth of 0.05. Thirty-seven out of 40 SCD ears and 18/58 normal ears were considered positive, resulting in a sensitivity of 93%, a specificity of 69%, a positive predictive value (PPV) of 67%, and a negative predictive value (NPV) of 93%. If the minimum notch depth was increased to 0.09, then we reached optimum specificity with 32/40
SCD ears and 16/58 normal ears considered positive for SCD, resulting in a sensitivity of 80%, specificity of 73%, a PPV of 67%, and NPV of 84% (see Table 3.4).

Effect of SCD size and air-bone gap on the PR notch size

Table 3.4: Summary of detection performance of the notch detection algorithm.

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<th>Minimum Notch Depth 0.09</th>
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<td>80%</td>
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<tr>
<td>Specificity</td>
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<td>72.4%</td>
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<tr>
<td>Positive Predictive Value</td>
<td>67%</td>
<td>66.6%</td>
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<td>Negative Predictive Value</td>
<td>93%</td>
<td>84%</td>
</tr>
<tr>
<td>Notch Detected for SCD Ears</td>
<td>37/40</td>
<td>32/40</td>
</tr>
<tr>
<td>Notch Detected for Normal Ears</td>
<td>18/58</td>
<td>16/58</td>
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3.2.3.3 Effect of SCD size and air-bone gap on the PR notch size

The anatomical length of the SCD determined from CT scans (n=38) varied between 1–7.8 mm. Linear regression analysis showed a marginally significant correlation (p=0.053) between SCD length and PR notch size. A significant correlation (p=0.008) was observed between the PR notch size and the averaged ABG between 250-1000 Hz (n=39; the ABG could not be computed in one ear due to a profound sensorineural hearing loss).

3.2.4 DISCUSSION

3.2.4.1 Power Reflectance

Power reflectance measurements are easy and fast using a relatively inexpensive FDA-approved device. Minimal training is required to insert an ear tip (similar to an earplug) into the ear canal, and to run the computer or control the machine. Two companies (Mimosa Acoustics and Interacoustics) provide FDA approved devices that measure PR. Both companies have various measuring devices that range in
price up to $10,000 USD. To further aid otologic diagnoses, various PR models can also perform otoacoustic emission measurements and simple tympanometry. Both companies work to incorporate research findings into diagnostic paradigms such as those of Nakajima et al. (12). The algorithm we present here could be internalized in their equipment to allow for automatic diagnostic estimates. We have no financial relationship with any company selling these instruments.

We demonstrated that an algorithm to sense notches in the PR measurements usually seen in SCDS has promise as a screening procedure for SCD. If SCDS is suspected based on this simple, non-invasive diagnostic test, then more costly, invasive and time-consuming diagnostic procedures (e.g. high-resolution CT scan and cVEMP) can be considered. This is particularly helpful for patients with non-specific auditory and vestibular symptoms that mimic other common pathologies. Furthermore, as shown in Nakajima et al. (12), if a patient has only a conductive hearing loss (without other symptoms), then PR in conjunction with the audiometric data can be used to differentiate between various causes of conductive hearing loss – ossicular fixation, ossicular disarticulation, and SCD. Thus, PR measurements can be utilized early in the assessment of a patient with vestibular and/or audiologic symptoms to reduce misdiagnoses, inappropriate treatment, unnecessary surgery and the need for more costly and invasive diagnostic procedures.

3.2.4.2 The Notch in PR

In most of the ears with CT-confirmed SCD and normal-appearing TM, the PR curves show a notch near 1 kHz. Depending on the parameters used to define the notch, our notch-detecting algorithm was able to provide separate SCD from non-SCD ears with sensitivities of 80% to 92%, specificities of 69% to 72%, NPV scores 84% to 93% and a moderate PPV score of 67%. The high NPV suggests PR with the proposed algorithm can be a useful tool in the initial diagnostic screening of patients with vestibular and/or auditory symptoms by ruling out SCD in patients with normal PRs.
However, there are limitations to PR. Power reflectance can be affected by the condition of the TM. An ear with normal audiogram but flaccid TM (sensed by tympanometry) may exhibit a notch similar to that seen in SCD (13). Power reflectance can also exhibit a notch in ossicular interruption, although the notch is more prominent and tends to occur at lower frequencies than in SCD, as Chapter 2 and 3.1 show (12). This study demonstrates that the PR notches detected by our algorithm can occur in normal ears (16–18 ears out of the 58 normal ears, resulting in specificity of 72% to 69%). Thus, our algorithm is suited as a screening tool due to its moderate specificity.

The PR notch near 1 kHz seen in ears with SCD is likely related to the effect of inner-ear dehiscence on cochlear impedance and ossicular motion. Such notches could result from a decrease in cochlear damping, which would exaggerate any TM-ossicular resonances and introduce a notch. Alternatively, a shift in middle ear resonance frequency due to a change in the total stiffness or inertance of the middle and inner ear can produce a peak or notch in the response referenced to normal mean. Future experiments in cadaveric temporal bones and computational models may aid in the understanding of the mechanism behind the significant effect of SCD on PR.

3.2.4.3 cVEMP Testing
cVEMP has been proposed for diagnosing various vestibular diseases as well as third window lesions such as SCD (15). Third window lesions have been associated with 10-20 dB decreases in low-frequency cVEMP thresholds (2, 5, 16-20). However, patients may have difficulty completing the testing if they have severe Tullio's phenomenon or limited neck motion. Furthermore, cVEMP responses vary with muscle mass, tone, activity, and fatigue and are greatly affected by movement artifacts (5). In this study, we noted that a significant fraction of our SCD ears (17/33) had normal cVEMP responses (95% confidence interval of normal ears).
3.2.4.4 **Effect of SCD size or air-bone gap on PR notch size**
In our series we only found a marginally significant correlation of SCD size with respect to PR notch size. On the other hand, significant correlation did exist between PR notch size and ABG. An increase in the PR notch size can be interpreted as a decrease in the impedance that the stapes experiences at the oval window. As the cochlear input impedance decreases due to the third window, the ABG increases due to the decrease in pressure difference across the cochlear partition (21, 8).
Somewhat surprisingly, in a larger series the size of the SCD correlated significantly with ABG (7), whereas we found that PR notch depth was significantly correlated with ABG but only marginally with SCD size. The methods for quantifying the ABG were similar in both studies. An increase in the number of PR measurements for SCD may resolve this seeming conflict.

3.2.5 **CONCLUSION**
This study provides evidence that PR in conjunction with a new algorithm to detect certain features in PR response can be used to screen patients for SCDS in the early stages of a diagnostic workup. If the PR is consistent with SCD, then more expensive and invasive diagnostic procedures can be considered. In addition, if a patient has a conductive hearing loss, PR can also differentiate between various causes of conductive hearing loss in an intact TM with aerated middle ear (12). PR can aid in the early stages of diagnostic workup to enable earlier diagnosis and prevent unnecessary treatment.

3.2.6 **APPENDIX: DESCRIPTION OF NOTCH DETECTION ALGORITHM**
The simple notch-detection algorithm relies on a few parameters that allow for variations in the notch shape and location. The specifics of the algorithm are described with the aid of Fig. 3.5 in the manuscript, which shows algorithm parameters along with features of a PR difference curve (the difference between an individual PR response and the mean PR of normal ears) for an SCD ear. First, the
algorithm searches for a local minimum in the PR difference curve within a specified
notch frequency range (underlined italics refer to parameters that can be optimized),
and designates this minimum point as the location of a potential notch (indicated by
a star in Fig. 3.5). Next, the algorithm finds the maxima on each side of the notch
occurring within the notch frequency range (marked as crosses in Fig. 3.5). The
notch depth (italics without underline refer to computed values) is computed as the
difference between the lower of the two surrounding maxima and the minimum
value in the notch (Fig. 2 is an example of the case where the upper-frequency
maxima is used to calculate the notch depth, illustrated by a vertical barred line).
Once the notch depth is computed, it is compared to the minimum notch depth to
determine if the notch meets the threshold depth criteria. Notches that are too wide
are eliminated by comparisons to the maxima found within a designated notch
frequency range.

Finally, the algorithm checks whether the identified minimum value of the V-shaped
notch is sufficiently less than the average of the difference curve over a specified
frequency range below the notch frequency. Specifically, the average value of the PR
difference curve is computed over a baseline range comprising frequencies from 1.5
to 0.5 octaves below the notch frequency. (The average over the baseline range is
shown as a thick horizontal bar in Fig. 2). This low-frequency “baseline” controls for
variations in the low-frequency PR in different ears. The difference between this
low-frequency average value and the value of the curve at the minimum “notch”
point is defined as the notch size (the example shown in Fig. 2 has a notch size of
0.294), and the minimum notch size parameter can be optimized. Both notch depth
and notch size were necessary for detection because the notch depth can be
calculated from either the low-frequency or the high-frequency maxima (as in the
example of fig. 2) and senses only whether this “notch” is deep and narrow enough
in a specific frequency range. On the other hand, notch size describes the depth of
the notch with respect to a low-frequency baseline value, which was useful in
optimizing notch identification in ears with SCD. We also tested for correlations
between notch size, SCD size and air-bone gap (discussed in a subsequent section).
We were able to adjust the three parameters (notch frequency range, minimum notch depth, minimum notch size) to distinguish between SCD and normal ears with high sensitivity and moderately high specificity. Detection thresholds of the above parameters were originally determined based on optimization around a subset of the data (26/40 ears) together with the normal population of 58 ears. The parameters were adjusted iteratively, and after each iteration, the sensitivity and specificity were evaluated and optimized. In defining notch frequency range the mean frequency of the SCD notch was used as the center, and the width around this center was widened until all of the SCD notches were present within this range. This resulted in a fixed notch frequency range between 585 and 1876 Hz. The effect of variations in minimum notch depth and minimum notch size on sensitivity and specificity were then evaluated by first setting one of these parameters to a fixed level. For example, before looking at the sensitivity and selectivity associated with variations in notch size, we fixed the minimum notch size, and all PR curves with notch sizes smaller than the minimum were assigned notch depths of zero. This exercise was repeated for the full collection of the 40 SCD ears with respect to the 58 normal control ears, resulting in the same optimized parameters, thereby demonstrating the strength of the selected parameter values. Fig. 3.6 A & B of the manuscript show receiver-operating characteristic (ROC) curves calculated for the 40 SCD ears and 58 normal ears for parameter variations. In Figure 3.6 A, we compare the use of notch size as a decision variable after first applying two different minimum notch depths. In Figure 3.6 B we look at the use of notch depth as a decision variable after first applying a minimum notch size. A minimum notch size on the order 0.1 and a minimum notch depth between 0.05 and 0.1 were found to separate most SCD ears from normals.

3.2.7 ACKNOWLEDGEMENTS

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3.3 Pre- and Post-Operative Measurements of Power Reflectance in Patients with Superior Semicircular Canal Dehiscence

The content of this chapter represent a preliminary manuscript that is being prepared for publication. The final publication will likely include additional patients and analyses, and others may contribute to those portions of this work. I have played a major role in all aspects of the work discussed here, and others have aided in the collection of the patient data.

3.3.1 INTRODUCTION

Patients with superior semicircular canal dehiscence (SCD) present a diagnostic challenge given the wide variety of signs and symptoms with which individual patients present, as discussed in Chapter 3.2. While mild in some patients and tolerable by avoiding symptom triggers (such as blowing ones nose), these symptoms can, in many patients, be incapacitating and substantially intrusive to daily lives (Silverstein et al, 2014). Fortunately, surgical management options are available which can significantly alleviate these debilitating symptoms (Crane et al. 2010), and as advances in the understanding and diagnosis of the pathology have increased, so have the surgical treatment options.

The most common surgical techniques involve resurfacing or plugging the dehiscence using either a transmastoid approach or a middle fossa craniotomy. The middle fossa craniotomy is advantageous as this approach provides direct visualization of the dehiscence and thus the dehiscence can be either resurfaced or plugged. However, the transmastoid approach, which only allows for plugging of the canal, is more familiar to most otologists and has lower risks of complications (such as CSF leaks). The downside to this approach is that it has a higher risk of post-operative vestibular hypofunction and the potential for cochlear or vestibular structures to be damaged (Yew et al, 2012, Agrawal et al 2009). Both of these approaches have been shown to provide significant post-operative relief of symptoms (Niesten et al 2012, Ward et al 2012, Crane et al 2010, Limb et al 2006).
Round window plugging, occlusion, and reinforcement are also currently being used as surgical management options as access to the round window provides the least invasive treatment. While not directly treating the dehiscence, or the pathological "third window", by altering the impedance at one of the other windows (thus reducing the "three" windows back to "two"), potential relief of symptoms is thought to occur (Silverstein et al, 2014). These round window approaches have been reported to provide relief in some patients, but the results are varied and the sample sizes are small (Silverstein et al 2014), and worsening symptoms have also occurred due to this procedure.

While substantial reports suggest that surgical management of SCD can result in alleviation of symptoms, there are also reports that show that not all symptoms are alleviated by surgery. Symptoms can return postoperatively and/or new symptoms can occur (Niesten et al 2012). Niesten et al (2102) performed a detailed analysis of pre-operative and post-operative signs and symptoms in 33 consecutive patients who underwent SCD repair and found that 100% of patients reported relief of their chief complaint postoperatively. However, after following up with patients over an average of 2 years, the authors found that a number of patients reported prolonged recovery and/or recurrence of symptoms, sometimes requiring revision surgery.

Given the general difficulty in initially diagnosing the presence of a dehiscence, the variety of surgical approaches, the variable results, and the invasive nature of most procedures, a non-invasive tool to diagnose and track patients pre- and postoperatively would be of clinical benefit, particularly in determining if a patient is a good candidate for a revision surgery. If a post-surgical patient returned complaining of new or recurring symptoms, comparison of an individual's pre-and post-operative results may provide insight into the potential cause for the reappearance of symptoms, such as a canal plug which is no longer adequately plugging the dehiscence. Given the distinctive notching pattern found in power reflectance (PR) measurements as a result of SCD (as discussed in Chapters 2, 3.1, and 3.2), this work served to explore how PR would change postoperatively as a
exploration into whether \textit{PR} may be a clinical tool which could be useful in tracking patients with SCD.

\subsection{3.3.2 METHODS}

A subset of the patients from Chapter 3.2, as well as additional patients, had \textit{PR} measurements made both prior to and after surgery. A total of 18 patients (10 females and 8 males) met the following inclusion criteria: a) pre- and post-operative \textit{PR} measurements, b) presence of SCD on CT scan preoperatively, c) absence of any middle-ear disease such as cholesteatomas, and d) absence of previous ear surgery for pre-operative measurements except for placement of tympanostomy tubes more than two years before measurement. The mean age was 46.5 years, ranging from 25 to 66 years old. Of these 18 ears, 12 were on the left side, and 6 on the right side. They were referred for \textit{PR} measurements from the Otologic Clinic at the Massachusetts Eye and Ear Infirmary between January 2010 and April 2014.

Preoperatively, patients underwent a battery of tests described in great detail in Chapter 3.2. Briefly, air and bone conduction testing were performed as well as tympanometry and acoustic reflex testing on most patients. VEMP testing was also performed on most patients.

Sixteen patients underwent surgery via middle fossa craniotomy (MFC), and two underwent surgery using the transmastoid (TM) approach. Table 3.5 displays detailed information on diagnostic and audiometric testing as well as signs and symptoms for each patient. The first line for each subject in this table details information regarding the patient preoperatively, whereas the second line notes information about changes in these results postoperatively, based on available data.

Overall, 13 patients reported complete resolution of symptoms related to SCD (although a few were diagnosed with benign paroxysmal positional vertigo (BPPV) or vestibular hypofunction, which can be side effects of the surgery and not reflective of the SCD). Five patients continued to complain of symptoms postoperatively to some degree, but the chief complaints varied between patients.
All 18 patients were included in our analyses regardless of whether their symptoms were completely resolved by surgery or not, but the possible effect of the lack of resolution of symptoms postoperatively is explored.

Power reflectance was measured with an FDA-approved commercially-available Mimosa Acoustic HearID system (Champaign, IL USA). Power reflectance measurements used wideband (0.2-6 kHz) chirp stimuli of 60 dB SPL intensity and three-second duration with individually calibrated acoustic systems as previously described in this work.

Table 3.5: Details of audiologic data. CHL is conductive hearing loss. First line for each patient is information resulting from the preoperative battery of tests as well as definitions of the type of surgery the patient underwent. The second line details the changes resulting from surgery as well as a summery grouping relating to symptoms either being resolved, somewhat resolved, or not resolved.
3.3.3 RESULTS

3.3.3.1 Comparison of Mean PR Data Preoperatively and Post Operatively

Figure 3.7 displays mean PR results +/- 1 standard deviation for measurements made prior to surgery (red) and following surgery (green). This figure also compares these means to our normal population mean +/- 1 SD. Similar to what we found in patients with SCD, these pre-operative measurements exhibit a notch, or a relatively sharp decrease, in PR around 1 kHz. Postoperatively, we observe an overall disappearance of the notch to nearly the same value as the normal within this frequency range. If you look closely at the lower range you can see that as a group, while the means are nearly normal around 1 kHz, the range postoperatively still has some features of a residual notch, indicating that not all measurements returned to relatively “normal” values. Two measurements are plotted in blue from the two patients who underwent surgery via the transmastoid approach. This data is included in the post-operative mean and range, but was plotted to demonstrate that there were no major observable differences in PR as a result of the approach type. While both individuals tend to have post-operative measurements on the stiffer side, they are also both almost completely within one standard deviation of the mean, and given the small sample size, we are unable to draw any conclusions as to whether this suggests any differences resulting from the two different surgical approaches. Given that these are not substantially different from individual post-operative measurements via middle fossa craniotomy, all post-operative measurements were treated as a group for further analyses, but in cases where individual data is shown, these two patients are similarly highlighted throughout.
Figure 3.7: Comparison of mean +/- 1 SD for all power reflectance measurements in 18 patients preoperatively (red) and postoperatively (green) with the mean +/- 1 SD of a normal patient population (n=58) from Chapter 2 and Rosowski et al 2012. The two blue dashed lines represent the two individual measurements from patients who had surgery via the transmastoid (TM) approach as opposed to the middle fossa craniotomy.

### 3.3.3.2 Comparison of Pre- and Post-Op Differences from Normal

Figure 3.8 and 3.9 display the differences from normal (the mean normal used throughout this work) of the pre-operative and post-operative PR measurements. Figure 3.8 shows the means of these individual differences +/- 1 SD while Figure 3.9 shows the individual differences (pre-operative data is displayed in red on the top, while post-operative data is displayed on the bottom). The post operative individual data is shown in green, with the differences for the two TM approach patients highlighted in blue and the differences for patients who reported some level of unresolved symptoms in black (the single purple curve represents a TM
approach patient who also had unresolved symptoms). Similar to what we found in Chapter 3.2, Figure 3.8 shows that when we consider the differences from normal, the notch near 1 kHz is very apparent in pre-operative SCD patients. Power reflectance measurements that are made after surgery in these same patients, however, show smaller differences from normal. Looking carefully at individual differences in Figure 3.9, many notches are apparent in individual data between 500 Hz and 1 kHz. Postoperatively, however, the general trend for most measurements is to surround the zero line with few notch-type patterns, suggesting these measurements are more similar to the normal mean than the pre-operative measurements. The TM approach patients and most of the patients with unresolved symptoms were spread out across the range of all of the individual data with no real trend; however, the largest postoperative notch is seen in a patient who had substantial postoperative symptoms (P143).

Figure 3.8: Mean +/- 1 SD of individual differences for both preoperative (red) and postoperative (green) PR from the normal mean.
3.3.3.3 Changes in PR Due to Surgery: Individual Pre-Operative Measurements Normalized by Post-Operative Measurements

An advantage of our work is that we compare pre and postoperative measurements in the same set of individuals. Figures 3.10 and 3.11 show the median +/- 1 SD and individual data of the ratio of preoperative and postoperative PR measurements. Ratios from patients with TM surgery are shown in blue, and patients with unresolved symptoms are highlighted in red. The one purple curve represents a patient who had unresolved symptoms and also had surgery via the TM approach.

If there were no measurable change in PR in an individual due to surgery, these results would show a flat line at zero. If an individual's postoperative PR was similar to a normal PR around 1 kHz, however, similar notches would be found in the ratio of preoperative to postoperative measurements as we find when comparing preoperative measurements to a population normal. Because of the presence of several
outlier results we constructed a median curve from the collection of median results at each of the measured frequencies. The median illustrated in Figure 3.10 clearly shows a shallow notch below 1 kHz. Observation of the individual ratio data in Figure 3.11 suggests that the individual results are more variable than what we saw in Figures 3.7 to 3.9. The notch is not quite as deep or defined as we see in Figure 3.8, and the individual measurements show substantially more fine structure than the pre-operative measurements in Figure 3.9. While one of the patients with unresolved symptoms shows a clear notch in the ratio consistent with the reversal of a large pre-operative notch, three show no change pre- and postoperatively (flat red and purple curves), and the largest outlier shows the opposite effect: this patient (P143) did not have a notch preoperatively but had one postoperatively. Furthermore, the notches seen preoperatively that were resolved with surgery (Figs. 3.9, 3.11) occur at varying frequencies, and these larger sharper notches are smaller and widened when the data is combined in the mean or median (Fig. 3.8, 3.10).

Figure 3.10: Median and 10-90% range for pre-operative measurements normalized by that same patients post-operative measurements.
Figure 3.11: Individual PR measurements preoperatively normalized by that same patients post-operative measurements. Post-operative measurements from the TM surgery are shown in blue. Patients with unresolved symptoms are highlighted in red. The one purple curve represents a patient who had unresolved symptoms and also had surgery via the TM approach.

3.3.3.4 Notch Detection Algorithm

Chapter 3.2 showed the utility of our notch detection algorithm in sensing SCD notches preoperatively. Here, we determine the results of this algorithm in our patient population both pre- and postoperatively. With a notch depth set at 0.9 and all other parameters the same as described in the previous section of this chapter, a notch was detected in 16 of the 18 (88%) preoperative PR measurements. This is slightly higher percentage than we found in Chapter 3.2. Notches were detected in 7 out of the 18, or 38%, of the postoperative PR measurements. This percentage is unchanged even if we do not include the 5 patients who had residual symptoms (5/13 or 38%). As a comparison, in Chapter 3.2, notches were detected in 29% of normal subjects. Postoperative PR measurements show a significant reduction in the number of detected notches, however, there is a higher percentage of notches detected in postoperative measurements than in the normal population tested in Chapter 3.2.
3.3.4 DISCUSSION

The surgical management and treatment of patients with SCD have variable results across patients as some patients report complete resolution of all SCD associated symptoms, while others may struggle with SCD related symptoms after surgery or even have worse or new symptoms. Unresolved symptoms could be the result of an unknown confounding pathology, as SCD symptoms mimic many common pathologies, the unmasking of symptoms in the contralateral ear due to bilateral SCD, or possibly a surgery in which the presence of the third window was not completely resolved. Side effects of the surgical procedure itself, such as dizziness due to BPPV or vestibular hypofunction, may also be confused with SCD related dizziness and balance problems. While surgeons can (and do) conduct revision surgeries, understanding the cause of recurrent symptoms could be of great use in tracking SCD patients postoperatively.

Our results show that as a whole, PR is sensitive to mechanical changes caused by surgery in SCD patients. This supports the idea that patients tend to be more mechanically “normal” postoperatively, and this also further backs the notion that the notch is a true and real effect of SCD, as it can be reversed when the pathology is reversed. As an SCD results in a PR notch in patients preoperatively, if the persistence of a pathological third window exists postoperatively, we hypothesize that PR would continue to be a sensitive indicator of this, and could help guide a surgeons decision to do a revision surgery or insight into the possible root of unresolved symptoms in an individual patient. While we do not have an adequate sample size of PR data in patients with unresolved symptoms in this work to explore the impact of these postoperative symptoms on PR, given the sensitivity of PR to changes caused by surgery, this question need further exploration.

3.3.5 CONCLUSIONS

This study suggest that PR has the potential to be a useful tool in not only diagnosing but also in tracking patients with SCD pre and postoperatively, particularly in
patients who may have recurring symptoms. PR measurements were sensitive to mechanical changes resulting from surgical management of SCD. Overall, our postoperative patient population showed “normalized” PR results when compared to preoperative data. Further studies including larger sample sizes of patients with recurring symptoms would be crucial in determining how PR can be used. Additionally, comparing surgical techniques such as plugging versus resurfacing will also be useful.

3.3.6 REFERENCES

3.4 Effects of Partial and Complete Ossicular Discontinuity on Mechanical Measurements

*This chapter was a collaborative effort. I contributed to all aspects of the study either actively or in a supervisory role. My major contributions included collection of a portion of the patient data, analyses of the power reflectance and the umbo velocity data, experimentation and analyses of temporal bone data, and substantial input to the theoretical design and development of this work. Major contributions to the analyses and interpretation of the air-bone gap measurements were made by coauthors of this work, which is being prepared for publication.*

3.4.1 INTRODUCTION

Another diagnostic challenge in conductive hearing loss that clinicians face is differentiating partial ossicular discontinuity versus complete ossicular discontinuity. Ossicular discontinuity, which is a separation of the middle-ear ossicles that most often occurs at the incudostapedial joint, may be complete, with no contact between the disconnected ends, or partial, where normal contact at an ossicular joint or along a continuous bony segment of an ossicle is replaced by connective tissue. While our population of discontinuity patients in Chapter 2 and 3.1 was small, we did notice some differences between the patients with a complete discontinuity as compared to the patients with only a partial discontinuity. There was a tendency for \( UV \) magnitude to be higher and the phase to change more abruptly and at lower frequencies for complete discontinuity when compared with partial discontinuity. In addition, air-bone gaps for the two patients with partial discontinuity across the frequency range of 250 to 4000 Hz was between 17 and 20 dB. However, for the four patients with complete discontinuity, the average air-bone gap across the frequency range of 250 to 4000 Hz was higher, ranging from 40 to 59 dB. Given these differences, we wanted to explore the effects of partial and complete ossicular discontinuity on various audiometric and mechanical measurements.

Ossicular discontinuity is generally diagnosed using a combination of audiometry and CT imaging, and is confirmed during middle ear surgery. However, it can be
difficult to differentiate a partial versus complete discontinuity even during surgery. The proximity of the disconnected ends and space-filling soft tissue (if present) makes visual determination of a partial or complete disarticulation a challenge, and even if it appears that a small amount of tissue is connecting the two disconnected ends, determination of the composition of this tissue and the amount of conductivity it provides is even more challenging (e.g. substantial fibrous tissue may provide a great deal of conduction whereas flimsy mucosal tissue may provide little to none).

In addition to our own observations of differences in audiometry for partial versus complete discontinuity, some suggest that the two types of discontinuity result in different patterns of conductive hearing loss (CHL) on audiometry. Specifically, a conductive hearing loss that is larger at high frequencies has been proposed as an indicator of partial ossicular discontinuity (Chien et al. 2008, Merchant et al. 2010, Sim et al. 2013). However, past studies have been hampered by the problems of separating out patients with partial and complete disarticulations.

The goal of this work was to determine the effects of both partial and complete discontinuity on audiometry, power reflectance, and umbo velocity. We first explored this in patients with either partial or complete discontinuity (as determined by information found in surgical reports). However, given the challenge of separating these pathologies even with direct visualization during surgery, and the amount of uncertainty as to the composition of any soft-tissue connections in partial discontinuities, we also explored the effects of these two pathologies in several controlled temporal bone preparations.

### 3.4.2 METHODS

#### 3.4.2.1 Patient Data and Methodology

Patient data was obtained in two different ways. Using the same methodology as in Chapter 2, patients with conductive hearing loss, an intact tympanic membrane (TM) and aerated middle ear that have not had surgery were recruited from the
Massachusetts Eye and Ear Infirmary otology clinic for UV and PR measurements. These patients also had audiometric data measured as a part of their normal otologic work up. There are a larger number of patients with UV data (n=29) than PR data (n=12) as the collection of UV data began before our group was making measurements of PR. Patients who were determined postoperatively to have a conductive hearing loss caused by ossicular discontinuity were then included in this study.

In addition, a query for ICD-9 diagnosis codes 385.23 (Dislocation of ear ossicle) and 385.24 (Partial loss ear ossicle) was performed on patients in the Massachusetts Eye and Ear Infirmary patient database from January 2008 to October 2013. Medical records from the resulting patients were retrospectively reviewed, and a total of 66 patients (for 66 ears) met the following inclusion criteria: 1) diagnosis of ossicular discontinuity confirmed during surgery, 2) absence of confounding pathologies, such as cholesteatomas, tympanic membrane lesions, and retrocochlear diseases, and 3) audiometry and operative notes on-file. While UV and PR measurements were not available for patient data collected from the database, it did allow us to substantially increase the amount of audiometric data we were able to consider (n=66).

We ultimately categorized the patients in two different ways, first by surgical report, and second by patterns in their air-bone gap measurements. Patients were separated into one of two categories, surgical partial or surgical complete discontinuity, based on the surgeon's operative notes and sketches. Patients were categorized as surgical partial discontinuity if their surgical reports included at least one of the following findings: 1) fracture of one or more ossicles, with no mention of ossicular erosion, dislocation, or separation, 2) partial dislocation of one or more ossicles (i.e., a fracture where bones remain in contact), with no mention of ossicular erosion, 3) complete separation at one or both ossicular joints, with mention of soft tissue spanning the interruption, or 4) erosion of one or more ossicles, with mention of soft tissue spanning the interruption.
Patients were categorized as surgical complete discontinuity if their surgical findings included a complete separation and/or at least one eroded or missing ossicle, with no mention of soft tissue spanning the interruption.

Categorizing patients based on retrospective review of surgical reports is challenging, and while every effort was made to categorize each patient accurately, the uncertainty in the presence of soft-tissue between the two disarticulated bones likely resulted in uncontrolled variability. Given this, we instituted a second classification scheme based on the audiometric results, as some have suggested that a CHL that is larger at high frequencies is an indicator of partial discontinuity (Chien et al. 2008, Merchant et al. 2010, Sim et al. 2013). Patients were separated into one of three categories based on air-bone gap (ABG) trends across frequencies: high-frequency CHL, which we hypothesize may represent patients with a partial discontinuity, large CHL, which we hypothesize may represent the population of patients with complete discontinuity, or other CHL, which consisted of patients who did not fit either category. Patients were categorized as high-frequency CHL if their mean ABG for 2-4 kHz exceeded their mean ABG for 0.25-0.5 kHz by 10 dB or more, and their mean ABG for 0.25-0.5 kHz was less than or equal to 20 dB. Patients were categorized as large CHL if their mean ABG for 0.25-4 kHz was greater than or equal to 40 dB. If a patient did not fit into these criteria, they were included in the other CHL category.

Umbo velocity and PR methods were the same in the above chapters. Briefly, laser-Doppler vibrometry (Polytec, Inc.) was used to measure UV. A laser beam was focused on the light reflex near the umbo of the tympanic membrane and a 9-tone stimulus was played into the ear canal. Simultaneous measurements of UV and the sound pressure near the tympanic membrane led to calculations of the ratio of the velocity to the stimulus sound pressure. See Chapter 2 and Figure 2.1 for more details.
Power reflectance responses to a wideband chirp stimulus from 0.2 to 6.0 kHz were collected using the Mimosa reflectance system with a sound source and microphone coupled to the ear canal via a foam tip. For each patient, two measurements were taken and averaged. Additional details can be found in Chapter 2.1 and Figure 2.2.

3.4.2.2 Temporal Bone Inclusion and Methodology

Six human cadaveric temporal bones were collected from donors with no known history of ear disease. The bones were either fresh or previously frozen. Laser Doppler Vibrometry was used to measure umbo, stapes, and round window velocity. A speculum was placed in the bony ear canal of the preparation and the reflector that had been previously been placed on the umbo was visualized with a surgical microscope. The coupler (a cylindrical apparatus similar to that used for the live-human measurements), which contained a probe-tube microphone and a speaker output, was coupled to a speculum. Seals were created with acoustic clay between the base of the speculum and ear canal, and at the top of the coupler and clear plastic coverslip. Sound stimuli were a series of single tones between 20 and 20,000 Hz presented between 70 and 90 dB SPL (this stimulus set has a significantly increased frequency resolution compared to the stimuli used in patients). The sound pressure in the ear canal was measured within 5 mm of the tympanic membrane. A laser beam from a laser Doppler vibrometer (Polytec Inc) was focused on reflective material placed on the umbo, posterior crus of the stapes, or round window. The normalized velocities are quantified as the ratio of the measured velocity to the measured sound pressure in the ear canal near the tympanic membrane. The ratio between the stapes velocity and the sound pressure in the ear canal is our measure of middle-ear sound transmission to the cochlea. In a subset of these bones (N=4), PR measurements were also made.

Measurements were made on the specimen in the completely disarticulated state (in which there was a gap of air between the incus and stapes), in a partially disarticulated state (in which there was a soft connection at the incudostapedial joint made with dental impression material (Jeltrate)), and in a fully articulated
state (in which the incudostapedial joint was in its original connected state, or was reestablished after disarticulation using dental cement). In some cases, different levels of articulation were achieved by using varied amounts of Jeltrate.

3.4.3 RESULTS

3.4.3.1 Categorization By Surgical Report

Patients were separated into one of two categories, surgical partial or surgical complete discontinuity, based on the surgeon’s operative notes and sketches. While each note or sketch varied in detail depending on the surgeon, they often reported soft tissue (including fibrous adhesions, mucosal bands, mucosal membranes, and scar tissue) spanning the point of ossicular disruption. However, operative reports rarely provided clarifying detail on the quality and stiffness of this soft tissue. As a result, we were often unable to conclusively determine if reported soft tissue created a mechanical connection that allowed for the transmission of sound. We decided to assume any soft tissue at a discontinuity might create a mechanical connection. While this likely means that the surgical partial discontinuity group includes patients who had soft tissue present that did not allow for the transmission of sound (and therefore mechanically acted as a complete disarticulation), there was no objective means to determine the degree of the partial disarticulation. However, it is more likely that the categorization of complete ossicular discontinuity was truly disconnected without the ability to transduce sound across the separated ossicles.

Figure 3.12 compares mean +/- 1 SD data for patients with partial discontinuity with complete discontinuity for the (A) air-bone gap, (B) umbo velocity, and (C) power reflectance. The mean ABG for the complete disarticulation group exceeds that of partial group at all frequencies. However, the hypothesized relationship between high-frequency CHL and partial discontinuity is not apparent. The mean ABG for the partial surgical group is quite flat and the ABG hovers near 30 dB across all frequencies. Figure 3.12 A & B show mean UV and mean PR results, respectively, for the partial and complete discontinuity groups. The UV data is almost identical
for the two groups; however, the mean PR for the complete group appears to have a notch of a slightly larger magnitude than that of the partial group. That said, there is significant overlap in the standard deviations between these two groups around the notch frequency range. Based on t-test calculations, differences in mean UV and mean PR results are not statistically significant at any frequency, suggesting the two groups exhibit similar middle ear mechanics.

Figure 3.12: Mean ABG, umbo velocity and power reflectance for partial discontinuity and complete discontinuity patient groups. The gray shaded region represents normative data +/- one standard deviation around the normal mean (from Rosowski et al. 2012).
3.4.3.2 Categorization by Audiometry

Individual Patient Results

Given the challenges of determining which patients fit into which disarticulation group based on surgical report, we decided to look at the patterns of the conductive hearing loss and create three groups: high frequency CHL, large CHL, and other CHL. Figure 3.13 displays individual ABG (top row), UV (middle row) and PR (bottom row) results for each group. Those who were part of the surgically-determined partial disarticulation group are shown using dashed lines.

For the ABG data (Fig. 3.13 A1) there were 8 patients who fit the high-frequency CHL criteria, and 7 (87.5%) were surgically categorized as surgical partial discontinuity. In contrast, there were 25 patients who fit the large CHL criteria, and 16 (64.0%) were surgically categorized as complete discontinuity (Fig. 3.13 B1). The majority of these patients exhibit greater ABGs in the lower frequencies, and many large CHL patients exhibit a peak at 2 kHz in the ABG curve (Fig. 3.13 B1). This 2 kHz peak is consistent with a Carhart's notch (due to a middle-ear lesion resulting in decreased bone conduction response around 2 kHz). Figure 3.13 C1 shows ABG data for patients that did not fit criteria for either high frequency or large CHL. This group includes 9 surgically-determined complete interruptions and 16 partial interruptions.

The second row of Fig. 3.13 (A2, B2, C2) displays UV data for patients with high-frequency, large, and other CHL, respectively. Overall, there do not appear to be substantial differences or trends that separate the two groups when looking at the individual data. The last row of Fig. 3.13 (A3, B3, C3) shows individual PR data. All high-frequency and large CHL patients exhibit a notch in PR between 500 and 800 Hz. However, many of the PR measurements of the other CHL group fall within or near the normal range and most do not exhibit a notch.
Figure 3.13: Individual patient data for groups sorted by ABG patterns. Columns A, B, & C show air-bone gap, umbo velocity, and power reflectance result respectively. Dashed lines represent patients categorized as surgically-determined partial discontinuity per the criteria detailed under "Methods"; solid lines represent patients categorized as surgically-determined complete discontinuity.
Mean Patient Results

Figure 3.14 compares the means of the individual data shown in the previous figure. Part A of the figure shows mean ABG results +/- one standard deviation for each CHL group. The separation between groups in the air-bone gap measurements in (A) is a direct result of the criteria required for inclusion into each group. Part B compares mean umbo velocity between the three groups. The mean UV of the large CHL group exceeds the mean UV of the high-frequency CHL group at all frequencies below 1 kHz; however, there is no significant statistical difference based on t-test calculations. Part C compares mean PR between the three groups. Power reflectance results between the high-frequency and large CHL groups have no statistically significant difference based on t-test calculations, and both show similarly shaped notches. However, it should be noted that the significance of such calculations are limited due to the small number of patients with PR measurements, particularly within the high-frequency CHL group (n=2). The mean PR of the other CHL group falls within normal range and does not exhibit a notch, despite the fact that the air-bone gaps for this group fall between the high-frequency CHL group and the large CHL group.
Figure 3.14: Mean patient air-bone gap (A), umbo velocity (B), and power reflectance (C) results by group based on ABG patterns. The bars on graphs A and B represent +/- one standard deviation from the mean. The gray shaded areas on the umbo velocity and power reflectance graphs represent normative data +/- one standard deviation around the normal mean.

3.4.3.3 Temporal Bone Results

Given the uncertainties in categorizing patients into the surgically-determined partial or complete groups, a temporal bone preparation was used to further explore the potential effects of the type of discontinuity. We explore the effects of partial and complete discontinuity on stapes velocity, which is used as a measure of the amount of conductive hearing loss caused by a particular manipulation on the preparation, and PR, as PR and UV measurements appear to provide similar results.
and PR has more potential for clinical utility due to its ease of use, cost, and FDA approval.

Stapes Velocity

Figure 6 displays the stapes velocity results for six temporal bone preparations with the ossicular chain in a partially disarticulated state, completely disarticulated state, and articulated state. Experiments grm038 and hhn166 have an additional manipulation which show stapes velocity (SV) with the chain in an almost articulated state. This almost articulated state was achieved by adding additional Jeltrate to the partially disarticulated state in order to create a stronger connection that would allow for a higher degree of sound transmission. All six preparations in the partially disarticulated state exhibit a drop in SV primarily at high frequencies, whereas the completely disarticulated state exhibit SV results that are larger and more consistent across frequency. These SV measurements in the complete disarticulation state are limited by the noise level of the laser vibrometry measurement device (these results are in the noise for all three cases). Thus, the actual "conductive hearing loss" caused by our total disarticulations may be larger than what is represented in these results. The two cases that include the almost articulated state, hhn166 and grm038 show that the degree of disarticulation may correlate to a graded response in the SV results, with larger losses resulting from smaller and less stiff connections.
Figure 3.15: Stapes velocity results for six temporal bone preparations. Bones grm010, grm018, hhn154, and grm036 show stapes velocity with the ossicular chain in a partially disarticulated state (dotted green line), completely disarticulated state (solid pink line), and articulated state (solid black line). Bones grm038 and hhn166 additionally show stapes velocity in an almost articulated state (dotted light green line), in which more Jeltrate was added to the partial state to create a stiffer connection.

**Reflectance**

Power reflectance measurements were also measured in four of the six preparations. Each preparation shows the results from a partially disarticulated state, completely disarticulated state, and articulated state, with the exception of grm038 which includes an additional nearly articulated state, as explained above. Regardless of the degree of the disarticulation, all PR results measured with any form of disarticulation exhibit deep notches between 500 and 800 Hz, as do two of the articulated conditions. There do not appear to be any substantial differences or trends between the nearly articulated, partial, and completely disarticulated states.
3.4.4 DISCUSSION

3.4.4.1 Clinical and Temporal Bone Results

This study explored the effects of partial and complete discontinuity on audiometric and mechanical measurements in both patients and temporal bone preparations. There is currently no test which can provide insight into the level of a disarticulation, and even determining whether a disarticulation is complete or partial with direct visualization at surgery is challenging.

When we separate patients with partial discontinuity based on surgical reports, we findaudiometry results that show slightly smaller air-bone gaps across all frequencies for partial discontinuity when compared to complete discontinuity, but these air-bone gaps do not show hypothesized high-frequency losses. This could be
a result of our criteria for inclusion into the surgically-determined partial group, as any mention of a soft tissue connection between the two disarticulated segments was considered a positive for inclusion. However, the composition of this connection is likely crucial to the transmission of sound across this gap, and in some cases, these surgically-determined "partial" patients likely have sound transmission equivalent to a complete disarticulation. Our two temporal bone preparations that displayed two different levels of partial disarticulations support this hypothesis as this data showed that the stiffer and more substantial the connection, the smaller the impact on the stapes velocity (or ABG).

Separating out the groups based on the pattern of the air-bone gaps, however, does support the high-frequency loss hypothesis for patients with partial discontinuity: even with the uncertainties in our surgery-based classification, 7 out of 8 (87.5%) of those who fit into the high-frequency CHL group were from the surgically-determined partial group, where as only 9 out of 25 (36%) of the patients who fit into the large CHL group were included this group. Our temporal bone data provides the most controlled test of this hypothesis, and consistently show high frequency losses resulting from the partially disarticulated state in contrast to large flat losses in the completely disarticulated state.

Regardless of the group an ear fell into, the effects of the different discontinuities appear to be similar on the non-invasive mechanical measurements explored in this work. Umbo velocity measurements show similar increases, or peaks, across the categorizations, and the distinctive notch is apparent in PR measurements regardless of the type of disarticulation. The only exception to this is in the PR measurements that fell into the "other CHL" group. Why these measurements appear more normal than any of the others is unclear, and could be the result of an additional unknown variable confounding the measurement (such as stiffer than normal tympanic membranes or the existence of a static pressure in the middle-ear cavity at the time of measurement), despite attempts to control for these types of
variables. We do not see any of these non-notch patterns in our well-controlled temporal bone preparations.

### 3.4.4.2 Comparison of Temporal Bone Results and Clinical Results

Direct comparisons of the SV changes in our six temporal bone preparations with the CHL loss between the high-frequency CHL loss and large CHL groups show striking similarities, particularly if you take into account the fact that the laser measurement device is limited by noise level and the hearing loss predicted in the case of complete disarticulation may actually be larger than we are able to record. Mean partial discontinuity SV measurements show a pattern similar to the high-frequency CHL group, with smaller ABGs at low frequencies and larger ABGs at higher frequencies. The complete disarticulation groups show larger ABGs across all frequencies. There is more separation between the groups at low frequencies and the means trend toward each other as frequency increases. This further supports the hypothesis that partial discontinuity can cause a CHL that is larger at high frequencies.

![Temporal Bone Results](image)

![Clinical Results](image)

Figure 3.17: (A) Change in stapes velocity with respect to the articulated (connected) middle-ear chain. The green line is the mean change due to partial disarticulation and the pink line is the mean change due to complete disarticulation in the temporal bone. Shaded regions represent +/- one standard deviation from the mean. (B) Mean ABG for high-frequency CHL and large CHL groups from Clinical section. Shaded regions represent +/- one standard deviation from the mean.
3.4.5 CONCLUSIONS

A conductive hearing loss that is of significantly larger magnitude at high frequencies appears to be indicative of partial ossicular discontinuity. If a patient has an ossicular discontinuity and exhibits high-frequency CHL, soft tissue that is capable of some level of sound transmission is likely present at the discontinuity. Seven of the eight patients with high-frequency CHL were categorized as partial discontinuity based on the surgical notes. However, the high-frequency CHL group included one patient with a surgically determined complete disarticulation and failed to capture 33 patients classified as surgically-determined partial disarticulations. This could be influenced by the difficulty in categorizing a patient into the two groups by operative reports, and the likelihood that at least some fraction of the surgically-determined partial disarticulations were connected by soft tissues that were too elastic to couple the ossicles in any useful manner. However, given that seven of the eight high-CHL were considered to be in the surgical partial group, high-frequency CHL as an indicator of surgical partial discontinuity (rather than complete) has high specificity (96%) but low sensitivity (18%). Umbo velocity and PR results suggest that high-frequency CHL and large CHL have comparable effects on middle ear mechanics measured at the ear canal.

This work suggests that when a CHL that is larger at higher frequencies is present, partial discontinuity should be strongly considered as a possible cause. Combining this audiometric information with a mechanical measurement such as PR, which is sensitive to discontinuity regardless of the level of articulation, may be able to provide confirmation of a suspected partial disarticulation in someone with a high-frequency CHL. These results are supported by experimental findings in a well-controlled temporal bone preparation.
3.4.6 REFERENCES

Chapter 4

Controlled Exploration of Reflectance in Human Cadaveric Preparations

The content of this chapter represent a manuscript that is being prepared for publication. I have played a major role in all aspects of this work.

4.1 INTRODUCTION

Otologic clinical practice makes limited use of assessments of middle-ear mobility to aid the diagnosis of middle-ear disease. Measurements of umbo velocity (UV) using laser-Doppler vibrometry (LDV) as well as reflectance (R) have been shown to aid in the non-invasive diagnosis of middle-ear disorders, as the last three chapters have described. Collectively, these data suggest that R shows potential in the non-invasive differential diagnosis of these pathologies.

Given the intersubject variability seen in both R and UV in normal, healthy subjects (as shown in Chapter 2 as well as in Keefe et al., 1993; Whittemore et al., 2004; Rosowski et al., 2012), knowledge of how the healthy normal ear responds, and then subsequently changes as a result of the development of a specific pathology, would provide the most controlled assessment of how these measurements are affected by pathology. While this cannot be done in patients who are only measured after the pathological change, a human temporal bone preparation gives us the ability to make measurements on a healthy, normal preparation, and subsequently manipulate the preparation to simulate middle-ear disease. Furthermore, reversal of the manipulation can ensure that measured changes were indeed caused by the manipulation. Limited reflectance measurements have been made on temporal bone preparations simulating various middle-ear pathologies including positive and negative static pressure, middle-ear fluid, ossicular fixations, ossicular discontinuity, and perforations (Feeney et al., 2009; Voss et al., 2012).
The goal of this work is to use a human temporal bone preparation to make reflectance measurements while simulating various pathologies that cause conductive hearing loss, including superior semicircular canal dehiscence. These measurements will be compared to measurements made on the same preparation using laser Doppler vibrometry at the umbo, stapes, and round window. This comparison allows us to further explore and explain the relationship between LDV measurements and R measurements, and gives us the ability to quantify the effect of a given manipulation, ensure the initial preparation is normal, and compare results to previously published data using similar simulations (Chien et al., 2007, Nakajima et al., 2005).

4.2 RESEARCH DESIGN AND METHODS

4.2.1 Human Temporal Bone Inclusion Criteria

Twenty-five human cadaveric temporal bones that appeared normal on microscopic evaluation were collected from donors with no known history of ear disease. Each bone was either fresh or frozen, and was prepared no more than 24 hours prior to measurements. If initial velocity measurements suggested the bone was abnormal (either because of suspected air in the cochlea, as determined by the ratio of the stapes velocity to the round window velocity at low frequencies, or abnormal ossicular motion), the bone was not used (Nakajima et al., 2005, Rosowski et al., 2007, Ravicz et al. 2000). Three bones were determined to have air in the cochlea and eight either had abnormalities to begin with or were damaged at some point during the experiment and were not used, resulting in fourteen temporal bones used in this work. Figure 4.1 shows the half cycle low-frequency phase difference between the stapes velocity and the round window velocity for all preparations used in this study (in black), as well as an example of one preparation (in dashed grey) that did not pass the air-bubble criterion.
Figure 4.1: Half cycle low-frequency phase difference between the stapes velocity and the round window velocity for all preparations used in this study (black), as well as an example of one preparation (dashed grey) that was excluded due to suspected air in the cochlea.

Preparation of the bone involved opening the facial recess and epitympanum to gain access to the malleus, stapes footplate, and round window. Small pieces of a reflective material were placed on the umbo, the posterior crus of the stapes, and the round window to improve the reflected light necessary for laser Doppler vibrometry.

4.2.2 Temporal Bone Manipulations

Initial velocity and reflectance measurements were made on the bone in the normal state, and repeated after each manipulation. The initial manipulation was a 2mm long 1mm wide opening drilled in the superior semicircular canal in order to simulate a superior semicircular canal dehiscence. Drilling was performed while the bone was immersed in saline in order to prevent the entry of air into the inner ear, and 1mm of saline was left over the dehiscence at all times. The dehiscence was
then patched with Jeltrate (dental impression material) in a manner to prevent entrance of air into the semicircular canal dehiscence. Malleus fixation was achieved by placing a rigid cylindrical bar of dental cement between the head of the malleus and the wall of the epitympanum. The bar was then removed in order to reverse the pathological simulation. Stapes fixation was achieved by covering the footplate of the stapes with dental impression material and/or super glue after drying the area. The size and strength of the malleus and stapes fixation manipulations varied, and stapes velocity measurements were used to determine the degree of each fixation produced by these manipulations, as changes in stapes velocity provide a quantitative estimate of the middle-ear transmission loss (a measure of conductive loss) produced by that manipulation. Finally, the incudostapedial joint was severed using a sharp scalpel to model ossicular interruption. Often, the lenticular process was severed to allow for an air gap between incus and stapes. All temporal bone preparations were frequently flushed with saline to ensure that the preparation remained moist. Some preparations involved some of these manipulations but not others. The fourteen total temporal bones used resulted in the following: stapes fixation (n=8), malleus fixation (n=10), ossicular discontinuity (n=10), and SCD (n=8).

4.2.3 Velocity Measurements
Laser Doppler Vibrometry was used to measure umbo, stapes, and round window velocity (see Figure 4.2). These measurements are similar in nature to $UV$ measurements made on patients using LDV in the previous chapters. A speculum was placed in the bony ear canal of the preparation and a reflector placed on the umbo and visualized with a surgical microscope. A plastic tube-like fixture coupled to a sound source and containing a probe-tube microphone was coupled to the speculum. The speculum was sealed to the ear-canal remnant in the bone using acoustic clay, and the top of the fixture, through which we viewed the umbo and directed the laser, was sealed by a glass coverslip. Sound stimuli were a series of single tones between 20 and 20,000 Hz presented between 70 and 90 dB SPL. The probe-tube microphone measured the sound pressure in the ear canal.
approximately 2mm from the umbo. A laser beam from a laser Doppler vibrometer (Polytec Inc) was focused on the reflective material placed on the umbo via the glass-backed fixture, posterior crus of the stapes, or round window via the open facial recess. The normalized velocities are quantified as the ratio of the measured velocity to the measured sound pressure in the ear canal near the tympanic membrane and the ratio between the stapes velocity and the sound pressure in the ear canal at the TM is our measure of middle-ear sound transmission to the cochlea.

Figure 4.2: Methodological set up for umbo, stapes, and round window velocity measurements in temporal bones using laser-Doppler vibrometry.

4.2.4 Reflectance Measurements

Pressure reflectance ($R$) is the complex ratio between the reflected pressure wave and the forward pressure wave. Pressure reflectance at a point in the ear canal is calculated from the impedance measured at that point, and the impedance is
calculated from the sound pressure measurement at that same point in the ear canal. The associated power reflectance ($PR$) is then calculated as the square of the magnitude of the pressure reflectance, $PR=|R|^2$, and is therefore a real number between 0 and 1, where 0 indicates that no energy is reflected and 1 indicates that all energy is reflected.

Reflectance measurements made in temporal bone preparations used similar methods to the same measures made in patients and described in the previous three chapters of this work. Briefly, $PR$ was measured using an Etymotic ER10C probe (containing a sound source and microphone) connected to software and hardware purchased from Mimosa Acoustics (HearID). For temporal bone preparations, these measurements were completed in an acoustic chamber to reduce noise interference, and the foam tip was secured into the bony ear-canal, which ranges from about 1-1.5 cm in length (see Figure 4.3). Five measurements were taken and averaged for every manipulation state.

![Reflectance measurement set-up for temporal bone preparations.](image)

Figure 4.3: Reflectance measurement set-up for temporal bone preparations.
4.3 RESULTS

4.3.1 Initial Normal Measurements

To evaluate the normality of our temporal bones, we compared the measured reflectance and velocity measurements at both the umbo and stapes to previously published normals made with similar preparations (Nakajima et al 2005, Whittemore et al 2004, Voss et al 2012). Figure 4.4 shows the initial normal reflectance measurements (n=14) for each preparation and a mean and range of one standard deviation (SD; A), as well as the median and interquartile (25% - 75%) range (B). The reflectance measurements are generally near one at the lowest frequencies (indicating that most of the power is reflected), and decrease with increasing frequency to a minima somewhere around 1kHz, although the magnitude of this minimum varies quite substantially. At frequencies above the minimum, the \( PR \) increases until around 4kHz, where the measurements tend to decrease somewhat again. These trends are similar to previously published normal data in cadaveric preparations (C; Voss et al 2012), although there are some noticeable differences, including lower low-frequency reflectance as well as some consistent higher reflectance in our data around 4 kHz. Our individual measurements show less fine structure at higher frequencies than those of Voss, despite the fact that the Voss data is smoothed using a seven point moving average filter and our data is not smoothed at all. These differences could be due to differences in the preparation. Unlike the Voss preparation, as our preparations have shorter ear canals and drilled out and widely open middle-ear cavities. The impact of these differences will be considered in the discussion.
Figure 4.4: A: Initial normal PR measurements for each preparation (n=14) (thin black lines) as well as mean (thick black line) and one SD range (gray shading). B: Initial normal PR measurements for each preparation (thin black lines) as well as median (thick black line) and 25-75% range (gray shading). C: Comparisons of median normal and range data for this work (black) and similar normal median and range from Voss et al 2012 (red).

4.3.2 Representative Data

To demonstrate the characteristic effects observed due to our simulations of pathology, Figure 4.5 shows all measurements made and calculated during a representative experiment. The collection of results from the normal state together with results after multiple simulated pathologies in the same bone allows us to directly observe the changes caused by pathology in a controlled way: a major goal of this work.
Figure 4.5: Magnitude and phase of reflectance, impedance, umbo velocity and stapes velocity from one representative experiment.
Figure 4.5 shows the magnitude of the $PR$ (A) and pressure reflectance phase (B), and compares these to the magnitude (C,E,G) and phases (D,F,H) of the impedance (calculated from the reflectance measurement), $UV$, and $SV$ for each manipulation. The initial measurement (solid black), reversal after SCD (dashed black) and reversal after malleus fixation (dotted black) are very similar demonstrating successful reversal of the effects of ossicular fixations. We see increases in $PR$ and impedance magnitude for stapes and malleus fixation from initial measurements at frequencies below 1 kHz. Similarly, we find decreases in umbo velocity in the same frequency range; however, there is a larger decrease in $UV$ for malleus fixation over stapes fixation, but a smaller decrease in $SV$ for malleus fixation than stapes fixation. After SCD, the $PR$ decreases at low frequencies and shows a shift in the minimum from around 1 kHz (normal) to about 600-700 Hz (SCD). There is a slight decrease and subsequent increase in the impedance magnitude, and slight increases in both the umbo velocity magnitude and phase. Changes of similar direction are found as a result of disarticulation, but the decrease in reflectance magnitude at the lowest frequencies is larger, the depth of the notch in reflectance is deeper, and the frequency of the notch is lower (500 compared to 1000 Hz). This is a trend that was observed before in Chapter 2. Phase data do not show consistent changes for most manipulations with the exception of disarticulation, which consistently shows a phase transition at the same frequency as the notch, in reflectance magnitude, or peak in umbo velocity magnitude. Note that post-disarticulation, the frequency of peak umbo velocity is very similar to the frequency of the sharp minimum in reflectance magnitude.

4.3.3 Mean Differences
To compare across various experiments, changes from the normal condition were calculated for each manipulation in each bone and averaged across bones. Figure 4.6 shows mean change from normal and the +/- 1 SD range for both $PR$ magnitude and pressure reflectance phase as well as the umbo velocity magnitude and phase for SCD (blue), the reversal back to normal after the SCD (black dashed), malleus
fixation (purple), the reversal back to normal after the malleus fixation (black dotted), stapes fixation (red) and disarticulation (green).

Figure 4.6: Mean change from normal for PR, pressure reflectance phase, UV magnitude, and UV phase for all manipulation states: SCD (blue), reversal of SCD (thin dashed black), malleus fixation (purple), reversal of malleus fixation (thin solid black), stapes fixation (red) and disarticulation (green).

These average changes are consistent with changes observed in the representative experiment (Figure 4.5), and are the focus of our attempts to separate the effects of the different pathologies on reflectance and umbo velocity measurements. One obvious difference is the depth (height) and sharpness of the notch (peak) induced change in the data after ossicular disarticulation. The decrease in sharpness and reduction in the depth or height of the extrema comes about from averaging
multiple curves with depths or peaks at somewhat different frequencies. While the magnitude of the increase in low frequency reflectance for the malleus and stapes fixation varies from experiment to experiment, when averaged, these changes show substantial overlap and become indistinguishable.

### 4.3.4 Changes Compared to Change in Stapes Velocity

In order to evaluate the effect the level of fixation had on the amount of change observed in the *PR* and the *UV*, comparisons of the change in stapes velocity (at 500 Hz: a good indicator of the magnitude of the conductive hearing loss) were made to changes in *PR* (from 500-700 Hz) and *UV* (at 500 Hz) from normal in Figure 4.7. Our umbo velocity measurements are very similar to previously published comparisons of fixation-induced changes in sound-induced stapes and umbo motions (Nakajima et al 2005). Malleus fixation produces reductions in umbo velocity that are more similar to the liked reductions in stapes velocity, while stapes fixations that produced 25 to 50 dB decreases in stapes velocity have little effect (at most -10 dB) on umbo motion (Figure 4.7). In reflectance, malleus fixation and stapes fixation can produce similar increases in *PR* magnitude, however the malleus fixation causes greater increases for a given amount of decrease in stapes velocity. This suggests a potential for separating malleus and stapes fixation based on the magnitude of the air-bone gap, but not based on *PR* results.

![Figure 4.7: Comparisons of changes from normal in UV (left) and PR (right) to SV changes.](image-url)
4.3.5 Comparison to Patient Data

These temporal bone measurements were performed to evaluate the changes produced by specific middle-ear pathologies, as measurements in human subjects and patients show substantial variations (Chapter 2; Rosowski et al 2012; Nakajima et al 2012). Nevertheless, PR measurements from specific temporal bones with simulated pathologies compare well to measurements made in individuals, as shown in Figure 4.8. Patient data is shown in dashed lines while temporal bone data is shown in solid. A mean patient normal from Rosowski et al (2012) is compared to the mean of the initial measurements from these preparations (black), with SCD comparisons in blue, stapes fixation in red, and disarticulation in green. We see similar notches observed for SCD and disarticulation in both patients and temporal bones, as well as similar increases due to stapes fixation.

That being said, there are noticeable differences between patient and temporal bone measurements. For example, the PR measured in temporal bones at frequencies above 2 kHz is generally larger than that measured in patients. These differences may be related to differences between our temporal bone preparation and live patient ears, e.g., in the temporal bones only the bony ear canal is present, and the mastoid cavities are widely open to the atmosphere. The potential impact of our preparation technique will be discussed later.
4.4 DISCUSSION

This work demonstrates the effects of malleus fixation, stapes fixation, disarticulation of the incudostapedial joint, and dehiscence of the superior semicircular canal on measurements of middle-ear function in a well-controlled temporal bone preparation. The simulated pathologies are representative of pathologies that cause conductive hearing losses in patients with intact tympanic membranes and well-aerated middle ears. Non-invasive pre-surgical diagnosis of which pathology is responsible for a CHL in these patients would be of great value. To this end, understanding how the different pathologies affect functional measurements will help determine whether such a separation of the different pathologies is possible and practically achievable. Clinical data has limitations:
functional measurements in pathological ears can only be compared to population normals, and there is a significant chance of uncontrolled variations between ears affecting the measurement independent of the pathology. The temporal bone preparation allows comparisons between initial "normal" measurements in each ear, and measurements made after well controlled and defined manipulations that mimic different pathologies. Furthermore, such preparations also allow observations of the effects of reversing the manipulation to better define a causal relationship between manipulation and effect. Such procedures lead to a significant reduction in uncontrolled variation in our investigations of the different pathologies.

Figures 4.5 and 4.6 demonstrate that both stapes and malleus fixations produce increases in reflectance and decreases in umbo velocity at frequencies below 1 kHz. These effects are consistent with mechanical stiffening due to the fixations. The malleus fixation was reversible; removing the cement between malleus head and the epitympanic wall returned the measured reflectance and umbo velocity to initial values, consistent with the fixation causing the changes in the measurements. We also found decreases in $PR$ (and increases in $UV$) around 1000 Hz for SCD and 750 Hz with disarticulation. These changes are likely the result of the introduction of resonances, perhaps due to a decrease in damping at the TM, as both a hole in the semicircular canal and a break at the incudostapedial joint decreases the load of the inner ear on the TM and ossicles. The disarticulation may also result in an increase in compliance, resulting in a shift (decrease) in the resonant frequency, which is not present in the SCD case (as the annular ligament is still present with SCD) and can explain why the resonances in disarticulation generally occur at lower frequencies than those seen for SCD. The decrease in damping introduced by discontinuity is greater than that caused by SCD, which may be why the notch for discontinuity is deeper in magnitude than the notch found due to SCD.

This is the first time $PR$ measurements of SCD have been made in temporal bones, however, similar measurements in various types of cadaveric preparations and in patients with some of these pathologies have been reported, and overall, our results
are quite similar. We find similar decreases due to fixation as previously reported for UV measurements in temporal bones, and our comparison of SV changes to UV changes in Figure 4.5 shows patterns similar to previous reports (Nakajima et al 2005). We also find overall similarities in PR for both stapes fixation and disarticulation to previous reports (Feeney et al 2009, Voss et al 2012).

In comparing our data to previous data measured in other temporal bone preparations and in patients, any potential differences introduced by our preparation procedure should be addressed. Figure 4.8 clearly demonstrates that the effect of the pathologies of interest on raw PR data with stimulus frequencies below 2 kHz are similar between our measurements and measurements in patients, but the increased reflectance at higher frequencies should be noted. Additionally, our normal measurements in Figure 4.4 show differences, including a lower reflectance below 1 kHz, from previously published temporal bones (Voss et al 2012). Unlike Voss et al (2012), our preparation included widely opened mastoid spaces to allow measurements of stapes velocity and manipulations of the ossicles. Such an opening removes the compliance of the middle-ear air spaces that restrains the motion of the TM (Zwislocki 1962, Møller 1965, Huang et al. 1997), and could result in a decrease in stiffness at the TM and lower PR at low frequencies. Additionally, a closed middle-ear cavity will produce additional resonances at frequencies above 2 kHz which add high-frequency fine structure to the middle ear input impedance and reflectance observed in Voss et al (2012). Voss et al (2008) explored the effects of opening the middle-ear mastoid cavity space and found low frequency decreases in reflectance as well as varied effects at high frequencies. In general, opening the cavity makes the Voss et al. measurements more similar to ours.

The open cavity in our preparation is common to both our normal and manipulated measurements, and it is possible that it will not affect the differences between these conditions (such as Figure 4.6). To investigate potential cavity effects, we conducted an experiment in which we manipulated the cavity condition (by repeatedly sealing
the cavity with silicone impression material (Westone) and reopening, while we manipulated the ossicular chain. Sealing the cavity in this manner may not mimic the live condition: we have drilled out the mastoid air cells and may have increased the middle-ear air volume; however, the temporal bones used in this work are removed as a bone plug and do not include the complete mastoid, raising the possibility that the enclosed air space is smaller than in a normal patient ear.

Figure 4.9 (left) shows comparisons of reflectance measurements made in a prepared temporal bone prior to any ossicular or inner-ear manipulation but with an open or middle-ear cavity. The differences produced by closing the cavity are similar to the differences between the normal temporal bone measurements in this study and those in Voss et al (2008). However, when you compare the difference between a measurement after a manipulation made with the cavity open to the initial measurement with the cavity open, and a measurement after a manipulation made with the cavity closed to the initial measurement made with the cavity closed, differences associated with cavity state essentially disappear (shown in Figure 4.9 right). Thus, differences in preparations and perhaps even between human subjects and temporal bones have small effects on the changes in reflectance produced by ossicular manipulations and pathology.

Figure 4.9: Left: Initial measurement made in a temporal bone with a cavity widely open (solid) and a sealed cavity (dashed). Right: Difference in PR between initial
measurements and malleus fixation (blue), stapes fixation (red), and disarticulation (green) when cavities are open for all measurements (solid) versus closed for all measurements (dashed).

One limitation of focusing on the changes from normal produced by a manipulation, as opposed to the raw data, is that in some cases these changes may not be representative of pathology depending on the individual initial measurement, as PR measurements are constrained from 0 to 1. For example, if a patient or temporal bone has a pre-fixation reflectance measurement (i.e. its individual normal) that is on the high end of the normal spectrum (close to 1), fixation of the stapes may not produce a large change in PR, because the normal PR is already so high. Umbo velocity measurements do not have an upper or lower limit in a similar way. This may be one reason that comparisons of changes in reflectance when compared to changes in stapes velocity (Figure 4.7) may not show as clear cut patterns as the umbo velocity measurements show when compared to stapes velocity.

4.5 CONCLUSIONS

In order to investigate the effects of pathologies such as those discussed in Chapters 2 and 3 in a controlled and systematic way, PR and other metrics of middle-ear performance were also measured in human temporal bone preparations with simulated pathologies similar to those of the patient populations. We report measurements human cadaveric temporal bone simulations of stapes fixation (n=8), malleus fixation (n=10), ossicular discontinuity (n=10), and SCD (n=8). These results are consistent with previous studies and are also strikingly similar to patient data. Given the level of control that we are able to obtain in these studies (as opposed to in clinical data), these results strongly support the clinical data findings and suggest that any uncontrolled variables did not significantly impact our results.
Chapter 5

A Novel Exploration of High-Frequency Reflectance in the Frequency Domain and the Time Domain

The content of this chapter represent a manuscript that is being prepared for publication. I have played a major role in all aspects of this work.

5.1 INTRODUCTION

The causes of conductive hearing loss are often difficult to determine accurately despite the frequent occurrence of various middle-ear diseases in the clinic (Merchant et al 1998). A non-invasive objective measurement that accurately distinguishes among various middle-ear pathologies in patients with an intact tympanic membrane and a conductive hearing loss would be valuable. Current clinical practice rarely utilizes assessment of middle-ear mobility to aid in the diagnosis of middle-ear disease, with the exception of tympanometry, which is usually measured at only one frequency.

Wideband acoustic immittance (WAI) measurements are non-invasive measures of middle-ear mobility over a wide frequency range. These measurements allow for the calculation of power reflectance (PR) or directly related quantities, such as absorbance. These quantities have been characterized in a variety of patient populations as well as in temporal bone experiments, as has been shown in the previous four chapters of this work. Collectively, these data suggest that PR shows potential utility in the non-invasive differential diagnosis of middle-ear and some inner-ear pathologies (Nakajima et al 2012, Rosowski et al 2012, Rosowski et al 2008, Feeney et al 2003, Allen et al 2005, Shahnaz 2009). However, due to frequency limitations in commercially available devices, WAI and PR have not been well described at frequencies above 6-8 kHz. Additionally, analyses of these
measurements up to this point have focused on the responses to stimulus frequencies below 3-4 kHz, while ignoring high-frequency or time-domain information.

A recent report from the Eriksholm Workshop on Wideband Absorbance Measures of the Middle Ear emphasized the need for time-domain analyses and stated that “Although the pressure reflectance phase has been reported in a number of early articles, there was consensus that the value of the temporal characteristics of WAI measurements has largely been ignored” (Feeney et al. 2013). To understand temporal characteristics, high-frequency information is required. In an effort to address these questions, this work uses a novel approach to measure PR that utilizes high-frequency signals and analyzes reflectance in both the frequency and the time domains.

Given the variability that exists in testing in clinical populations, we use a controlled temporal bone preparation to determine if high frequency reflectance measurements analyzed in both the frequency and time domain is useful in the differential diagnosis of conductive pathology. While phase data in current reports of reflectance have been shown and could be used to begin to explore temporal characteristics, the frequency resolution of these measurements is insufficient for analysis in the time domain. The expanded frequency range we use in this work (20 Hz to 20 kHz) will provide additional information in the frequency domain and provide the temporal resolution needed to quantify potential pathology-induced changes in the time domain reflectance (TDR).

We used a custom built sound source (the HARP system designed by J. H. Siegel at Northwestern University) in consort with an ER-10B probe tube microphone (Etymotic Research). This custom acoustic system delivers stable high-frequency sounds with little crosstalk between the stimulus and microphone signals. Experiments were performed with fresh human cadaveric preparations, which allowed for the serial introduction of well-controlled simulated pathologies. Several
of the pathologies could also be reversed. Experiments on temporal bones also allow for accurate determination of the effects of simulated pathologies because the normal initial state can be measured for each bone.

5.2 RESEARCH DESIGN AND METHODS

Given the novelty of our custom-built high-frequency reflectance measurement system, a significant portion of this work went into developing and evaluating our analytical methodology. This work was thus split into two phases; the first "development" phase involved four temporal bone experiments in which we made measurements of reflectance using both the Mimosa system (used in the previous four chapters) as well as the HARP system in the same preparation. We used these comparisons to test the validity of the analytical methodology used in the data collected with the HARP system. This also allowed for direct comparisons of the two systems (in the frequency ranges which overlapped). In the "measurement" phase, we made reflectance measurements using the HARP system in 5 temporal bones with manipulations simulating pathologies. We glued the foam ear-tips into our preparations in these experiments to control for any variability that could be introduced by removing and reinserting the tips.

5.2.1 Calibration of Reflectance Technique

Because the impedances of ear canals are unknown, the Thévenin equivalent of the sound-delivery system must be computed. This is done through a calibration procedure in which pressure measurements are made in four cavities with known acoustic impedances. These four cavities provide four complex equations from which we can then calculate the two unknown Thévenin equivalents of the source, the Thévenin Pressure and the Thévenin Impedance (Allen 1986, Figure 5.1). While using two equations to solve for two unknowns would be sufficient, the use of four equations provides over-determined solutions in order to minimize calibration errors using a least squares best fit analysis.
Sound pressure measurements were made in four cylindrical tubes in response to linear wideband chirps from 20 Hz to 20 kHz. In order to determine the acoustic impedances of these tubes, the quarter wavelength resonances were used to estimate acoustic lengths. The acoustic lengths combined with the known radius of each cylindrical cavity were then used to determine the acoustic impedance of each tube (Keefe 1984). Once the acoustic impedances of these cavities are known (i.e. \( Z_{load} \) in Figure 5.1), the unknown Thévenins can be calculated.

**Thevenin Equivalents Circuit**

![Diagram of Thevenin Equivalents Circuit](Figure 5.1: Thévenin equivalents circuit used in calibration technique)

This calibration technique is essentially the same as the reflectance calibrations made in Chapters 2 through 4, however, the Mimosa system used to measure reflectance in these chapters automatically calculates these Thévenins. The use of this novel system required development of our own custom software to accomplish the same tasks. The first step in evaluating our results was to determine that our Thévenin equivalents were adequate. Figure 5.2 displays the results of this analysis from our four “development” phase experiments. The four panels show the calculated Thévenin pressure and impedance magnitudes and phase angles for the
four calibrations, and demonstrate that our system produces stable calibrations across various experiments with differing foam tips.

![Figure 5.2: Thévenin pressure and Thévenin impedance magnitude and phase from the calibrations associated with the four "development" phase experiments.](image)

The next step of the evaluation used the Thévenins to calculate the impedance of the longest cavity. We did this by using the Thévenins from a specific experiments' calibration combined with the measured pressure from the longest calibration cavity of the same experiment to calculate the impedance of that cylindrical tube (Figure 5.3). Since we knew the tube's theoretical impedance, this was a simple test of the system. These results are shown as the first four curves in Figure 5.3. However, since the measured pressure used to calculate the cavity impedance was also used in the calibration for that same experiment, this was not an independent test.

To explore the stability of our Thévenin source characteristics in a more independent way, we also calculated the longest cavity's impedance magnitude and phase from a sound pressure measurement made in one experiment (grm020) with
the Thévenin equivalents calculated in another (grm017), the result of which is shown in a grey dashed line in Figure 5.3. We found the result of this more independent test to be very similar to the result using both the calibration and sound pressure measurement from the same experiment, although you can observe some differences, particularly in the phase changes at frequencies above 6 kHz. These differences may result because the acoustic length of the tube is slightly different between the calibration and the measurement.

Figure 5.3: Impedance magnitude and phase for the longest cavity of the calibration tubes for all four experiments. For four of the five cases, the calibration for that same experiment was used. The dashed grey line represents a case that used the calibration from grm017 to calculate the impedance of the longest tube from data gathered in experiment grm020.

5.2.2 Calibration Error Evaluation

The Mimosa HearID software rejects calibrations that are not within an acceptable range. Errors can occur due to a leak in the foam ear-tip, obstruction of the speaker, obstruction of the microphone tubing, or excessive noise in the measurement. We evaluated each of our calibrations with an error function that quantifies the deviation between measured and reconstructed cavity pressures. We determine the load impedance from the estimated acoustic lengths (and the Thévenins), and then reconstruct the cavity pressures from the load impedance (and the Thévenins). We then adjust the acoustic lengths (iteratively) to minimize the deviation between measured and reconstructed pressure. The error value quantifies the deviation between measured and reconstructed cavity pressures and is scaled to make any
error < 1 acceptable. All calibrations used in this work meet the criteria of having calibration errors less than 1.

5.2.3 Reflectance Measurements
Pressure reflectance \( R \) is the complex ratio between the reflected pressure wave and the forward pressure wave. Pressure reflectance is related to the measured impedance by the following equation:

\[
R(f) = \frac{Z}{\rho c / A} - 1
\]

\[
R(f) = \frac{A}{Z} + 1
\]

where \( f \) is frequency, \( Z \) is the ear-canal impedance, and \( \rho c / A \) is the characteristic impedance \( (z_0) \) where \( \rho \) is the density of air, \( c \) is the speed of sound in air, and \( A \) is the cross-sectional area of the ear-canal. The frequency-domain permutation of \( R \) that is considered in this work is the power reflectance \( (PR=|R|^2) \). Reflectance measurements are collected using a custom-built sound source (the HARP system) in consort with an ER-10B+ probe tube microphone (Etymotic Research) coupled to the temporal bone by a foam tip inserted into the ear canal. Wideband linear chirps with a bandwidth of 20 Hz to 20 kHz were generated from custom software (written by M.E. Ravicz in LABVIEW) and used as the stimulus. Measurements were completed in a sound-proof chamber. All data were analyzed using MATLAB.

5.2.4 Time Domain Analyses
Time-domain descriptions of reflectance are obtained from the inverse Fast Fourier Transform (iFFT) of the measured frequency-domain pressure reflectance. The amplitude of the time-domain reflectance \( (TDR) \) is defined by the dimensionless output of the iFFT multiplied by the sampling rate; this multiplication makes the \( TDR \) peak values independent of sampling rate, and gives the \( TDR \) units of frequency. Thus, the area under the \( TDR \) curve (over some interval of time) is dimensionless and indicates the fraction of the forward wave that is reflected within
that time interval. Time-domain reflectance can be either positive or negative depending on the instantaneous phase of the reflected pressure relative to the forward pressure.

5.2.5 Surge Impedance

One significant difference in the analysis of reflectance in this chapter involves the characteristic impedance, $z_0$, used to calculate reflectance. The characteristic impedance is a quantity dependent upon physical characteristics such as the cross-sectional area of the ear-canal at the location of the impedance measurement and generally assumes that the canal is a uniform tube. However, the cross-sectional area of the ear canal varies along the length of the canal, so the uniform tube model of $z_0$ is not completely accurate. Surge impedance is defined as the impedance in time at time zero, and is derived from measurements rather than physical characteristics. In cases where $z_0$ is completely accurate (such as in the case of a uniform tube), the surge impedance and the characteristic impedance are equivalent. However, in ear-canals, where non-uniformities are present, the surge impedance may be more accurate than $z_0$.

All previous reflectance analyses considered in this work use the same estimate of an average adult ear-canal diameter for calculations of characteristic impedance. However, a mismatch between the physical cross-sectional area of the ear canal at the precise measurement location and the cross-sectional area used in the calculation can lead to an error in the calculation of the $TDR$ at time zero. This error appears as a spurious reflection at time zero due to a mismatch between the surge impedance and $z_0$. Using the surge impedance from our TDR calculations instead of $z_0$ (calculated with an average ear-canal diameter) results in a better estimate of the ear canal. Thus, this surge impedance is used in our calculations of $R$, $PR$, and $TDR$. The influence of the surge impedance will be discussed.

Our assumption that the reflectance at time zero should be zero is easily realized in cases where the residual ear canal length (from ear-tip to tympanic membrane) is
1.5 cm or longer, and there is a ready separation of any spurious 'reflection' at the canal entrance and 'true' reflections from the TM. However, our temporal bone preparations usually only retain the boney part of the canal, which is typically 1 cm in length, and much of this length is filled with the foam ear tip. The shorter travel time between the ear-canal entrance and the TM reflections mixes reflections from the ear canal and the TM due to the limited bandwidth of the measurement and can produce non-zero reflectances at time zero. Thus, requiring the TDR to be zero at time zero can alter the estimated reflection from the TM. While we could have decided to maintain longer natural ear canals, or artificially lengthen the canal, determining a solution to this problem would assist investigations in ears with naturally short ear canals, e.g. infants. Thus, for this work, we estimate a "non-surge" contribution to the TDR at time zero from the load impedance (Neely, unpublished). The amount by which the TDR at time zero exceeds this non-surge contribution becomes the estimate of the surge impedance.

We confirmed the use of this new methodology for estimating the surge impedance in "short" ear canals experimentally. We attached a 10 mm artificial ear canal to the boney ear canal of a temporal bone preparation. The resulting ear-canal length was approximately 21 mm (to the umbo). The artificial ear canal was sealed to the boney ear canal with silicon impression material (Westone). Reflectance measurements were made using the HARP system and a wideband chirp stimulus (20 Hz-20 kHz, 100 averages). The reflectance was calculated using the surge impedance estimation routine "A" (which requires the TDR=0 at time zero) as well as the new estimate of the surge (routine "B"), which included an estimate of the non-surge contribution to the TDR at time zero. We calculated the cross-sectional area from the resulting surge impedances. If the new routine "B" worked as expected, the surge impedance estimated from the two routines should be equal. We also physically measured the artificial ear-canal diameter and calculated its cross-sectional area for comparison of estimated cross-sectional areas to physical measurement of the same area.
The areas are as follows:

\[ A \text{ (by physical measurement)} = 3.1174 \times 10^{-5} \, \text{m}^2 \]
\[ A \text{ (w/surge routine "A")} = 2.9167 \times 10^{-5} \, \text{m}^2 \]
\[ A \text{ (w/surge routine "B")} = 2.9525 \times 10^{-5} \, \text{m}^2 \]

The two 'surge' calculations give similar area estimates but underestimate the physical measurement by 5 - 7%. This degree of error in characteristic impedance results in a change in \( PR \) of less than 0.001, and is within the error of our estimates.

### 5.2.6 Velocity Measurements

Laser Doppler Vibrometry was used to measure umbo, stapes, and round window velocity. All three velocity measurements were used to determine if the velocities in each preparation were similar to published normal data (as done in Chapter 4) in all temporal bone preparations in both the “development” phase and the HARP “measurement” phase. A laser beam was focused on reflectors placed on the umbo or the posterior crus of the stapes, and a series of single tones between 200 and 20,000 Hz were played into the ear canal. The resulting velocities of either the umbo or the stapes are referenced to the measured sound pressure in the ear canal near the tympanic membrane. Round window velocities were measured and showed half cycle phase-angle differences from stapes velocity at frequencies below 500 Hz, consistent with an air-free fluid-filled inner ear.

For the four temporal bones used in the development phase, both umbo and stapes velocities were measured after every manipulation (in addition to both HARP and Mimosa measurements). This allowed for determination of the changes induced by the manipulations, and for comparisons to previous data. Small differences could result from inserting, removing, and reinserting the reflectance probe tip (due to small variations in the position of the probe, the seal of the probe foam tip, and the expansion of the foam tip).
In the five experiments with just the HARP system, after velocity measurements determined that the bone was normal, the HARP foam probe tip was glued into the bony ear canal with dental cement. Gluing the tip provided stability and consistency of the probe tip location and ear-canal seal throughout all manipulation states, but did not allow for the measurements of umbo velocity. We still were able to measure stapes velocity to assess the effect of manipulations on middle-ear transmission. A difference from earlier stapes velocity measurements is that the HARP system sound source and microphone are farther from the TM than in the typical LDV set-up, but stapes velocities measured using this technique showed little difference from those made with the standard LDV sound source and microphone. Figure 3.15 from Chapter 3 compares stapes velocity measurements using the standard LDV sound source and microphone (grm010, grm018, hhn166, hhn154) and the HARP source and microphone (grm036, grm038).

5.2.7 Temporal Bones

All measurements were made on human cadaveric temporal bones. The donors had no known history of ear disease and the ears appeared normal during microscopic evaluation. Each bone was either fresh or previously frozen, and was prepared no more than 24 hours prior to measurements. Preparation involved opening the facial recess and epitympanum to gain access to the malleus, stapes footplate, and round window.

5.2.8 Manipulations

Initial umbo and stapes velocity compared favorably to previously established acceptable normal values, as explained above. Measurements of reflectance and stapes velocity were made after fixing the head of the malleus to the surrounding bone with a bar made of dental cement, after reversal of the malleus fixation (removal of this bar), after fixation of the stapes footplate with dental cement, and finally after disarticulation of the incudostapedial joint. For comparisons of HARP and Mimosa measurements made during the development phase, the two sources were removed and reinserted before and after each manipulation.
5.3 RESULTS

5.3.1 Frequency Domain Results

5.3.1.1 Representative Experiment

Figure 5.4 shows representative PR results from 20 Hz to 20 kHz from the HARP measurement device made in a single preparation from the measurement phase. Initial normal measurements are shown in black, malleus fixation in blue, reversal of the malleus fixation in dashed black, stapes fixation in red, and disarticulation in green. We find PR increases above normal in both stapes and malleus fixation from 200 to 1000 Hz. We also noticed some small differences between stapes and malleus fixation at the PR peak around 6 kHz, where stapes fixation seems to be above normal, and malleus fixation seems to be below normal (note the good reversal of malleus fixation). We also find the characteristic large notch in PR around 650 Hz after ossicular disarticulation. Above 6kHz, we do not observe any consistent differences between the manipulation states.

![Figure 5.4: Power Reflectance results in a representative human temporal bone experiment measured with the HARP system. Each experiment has an initial measurement, as well as measurements of malleus fixation, reversal of malleus fixation (dashed), stapes fixation, and disarticulation of the incudostapeidal joint.](image-url)
5.3.1.2 Mean Results

The top figure of Figure 5.5 displays the mean $PR +/ - 1$ SD range for normal (black), malleus fixation (blue), reversal (gray), stapes fixation (red), and disarticulation (green) made in the measurement phase. The bottom figure shows mean change for each of the same manipulation states from the initial normal mean. Both stapes and malleus fixation result in increases in $PR$ between 400 Hz and 1-2 kHz. Ossicular discontinuity generally presents as a sharp notch in $PR$ between 600 and 900 Hz. Individual data (such as that shown in the representative data in Fig. 5.4) exhibit larger, sharper notches at somewhat varied frequencies that are smoothed by the averaging used in calculating the mean.

5.3.1.3 Surge Impedance

Theoretically, the estimated surge impedance in the measurement phase (with glued-in sound sources) should be consistent across manipulation state. A test of our surge impedance technique is to consider how the surge impedance varies in an individual preparation. For example, the surge impedance estimates for GRM031 were as follows:

- Initial=5.46x10$^{06}$ ohms
- Malleus Fixation=5.6x10$^{06}$ ohms
- Reversal=5.41x10$^{06}$ ohms
- Stapes Fixation=5.65x10$^{06}$ ohms
- Disarticulation=5.55x10$^{06}$ ohms

The average of these surge impedance estimates is 5.5340x10$^{06}$ ohms, and the standard deviation is 0.0986x10$^{06}$ ohms (or +/- 1.8% of the mean). Overall, the surge impedances were comparable within single preparations across all manipulation states (varied less than +/- 3%), and no significant differences were found between estimated surge impedances across manipulations for any preparation.
5.3.1.4 Frequency Domain Statistical Analyses

Analyses of variance (ANOVA) found significant differences in the “measurement” phase $PR$ averaged over the 400 to 1000 Hz range between initial measurements and malleus fixation ($p=0.0403$) as well as between initial and disarticulation ($p=0.0209$), but not between initial and stapes fixation ($p=0.0945$). Significant differences were also found between disarticulation and both malleus ($p=0.0001$) and stapes ($p=0.0004$) fixation. As expected, no significant differences were found between the normal and the reversed malleus fixation measurements. No significant differences occur between stapes and malleus fixation in any frequency range, although there is a trend in the mean data around 1500 Hz that shows increased $PR$ for malleus fixation when compared to stapes fixation. No manipulation related differences in $PR$ were discernible at frequencies above 4 kHz.

![Mean Power Reflectance](image-url)
Figure 5.5: Power Reflectance means +/- SD (top) and mean differences +/- SD from initial (bottom) for the above 5 HARP experiments.

5.3.1.5 Comparison of Frequency Domain HARP Results to Mimosa Results from Chapter 4

Figure 5.6 displays the mean changes due to manipulations measured by the HARP system (during the measurement phase from Figure 5.5, solid lines) with mean differences for these same manipulations made in separate preparations with the Mimosa device (data from Chapter 4, Figure 4.6). Collectively, the data suggest that in overlapping frequency ranges (200 Hz to 6 kHz) changes due to manipulations are similar, whether measurements are taken with the Mimosa or HARP device, and that the HARP device does not add additional frequency-domain information for differential diagnosis. There are some notable differences around 4 kHz, where the Mimosa measurements with stapes fixation appear higher than HARP measurements and potentially separable from other manipulations.
5.3.2 Time Domain Results

5.3.2.1 Representative Experiment

Figure 5.7 shows the time-domain reflectance \( (TDR) \), computed from the pressure reflectance in a representative experiment (the same representative experiment shown for frequency-domain responses above in Figure 5.4). Initial normal measurements are shown in black, malleus fixation in blue, reversal of the malleus fixation in dashed black, stapes fixation in red, and disarticulation in green. Time-domain reflectance is non-zero at time zero due to the temporal resolution and the initial reflectance from the eardrum in our short ear canals (as explained in the methods regarding surge impedance). We observe a large initial peak in \( TDR \) at \( t=0.075 \) ms in all manipulation states, which is due to the reflection at the eardrum.
This is followed by a decrease in the TDR with a minimum near 0.14 ms. This TDR minimum is similar in amplitude in the normal, disarticulated, and stapes-fixed states, but is not as deep in malleus fixation. At longer time intervals the TDR rises and remains near zero, with some manipulation related differences in fine structure. The TDR in both malleus and stapes fixation is increased compared to normal between 0.2 and 0.3 ms delay, while the disarticulation TDR is below normal at this same time. We see a small dip in malleus and stapes fixed TDR near 0.6 ms and an increase in disarticulated TDR from 0.55 to 1 ms.

![GRM037 TDR](image)

Figure 5.7: Representative Time Domain Power Reflectance (TDR) computed from the R measured with the HARP system. Each experiment has an initial measurement (black), as well as measurements of malleus fixation (blue), reversal of malleus fixation (black dashed), stapes fixation (red), and disarticulation of the incudostapeidal joint (green).

### 5.3.2.2 Mean Results

The top figure of Figure 5.8 displays the mean time domain reflectance +/- 1 SD range for normal (black), malleus fixation (blue), reversal (black dashed), stapes
fixation (red), and disarticulation (green). The bottom figure shows mean change for each of the same manipulation states from the initial normal mean. The changes observed in the mean PR are similar to those described for the representative data of Figure 5.7. Considering the changes from normal in the bottom panel allows us to focus closely at changes due to manipulations. All manipulations (but not the reversal condition) appear to result in a small non-significant reduction in TDR at very short latencies, and have normal TDR values at the time of the peak from the ear-canal (t=0.075ms). At longer time intervals, TDRs increase for both malleus fixation and stapes fixation, with the malleus fixation increases being larger and occurring earlier in time. Ossicular discontinuity results in a short latency (0.2 ms) decrease in TDR followed by an increase in TDR. The first major separation between manipulation states that we notice in time is an increase in malleus fixation TDR just prior to 0.2ms. The next notable change is in disarticulation, where we see decreases in TDR just after 0.2ms. Finally, we see increases in TDR for stapes fixation just after that, near 0.25ms, although this increase is smaller than the observed increase due to malleus fixation.

5.3.2.3 Statistics of Time-Domain Analyses

For the TDR means (Figure 5.8, top), statistically significant differences occur between disarticulation and all other states in the 0.2-0.3 ms time range, but no other significant differences appear in the means. If we average the change from initial TDR for each manipulation (Figure 5.8, bottom), there are significant differences near 0.1375 ms between malleus fixation and all other pathologies, including stapes fixation (p=0.0031). This is the only reported significant difference found between malleus and stapes fixation using reflectance measurements alone.
Figure 5.8: Time Domain Reflectance means (top) and mean of the differences from initial (bottom) from the 5 measurement phase HARP experiments.
5.3.3 Comparison of HARP and Mimosa Systems

5.3.3.1 Individual Comparisons

Figure 5.9 compares individual PR between HARP (solid) and Mimosa (dashed) for two examples of the four development phase experiments. There is a trend for the Mimosa measurements to produce slightly lower PR at frequencies below 500 Hz, and higher PR above 2 kHz. In some cases, the Mimosa measurements exceed 1, which we have seen in temporal bone experiments before in Chapter 4. While the Mimosa measurements are higher between 4 and 6 kHz (the upper limit of the frequency range for the Mimosa measurements), the general frequency dependence of PR is similar in the HARP and Mimosa measurements.

Figure 5.9 (A-H): Individual comparisons of initial measurements as well as measurements of malleus fixation, stapes fixation, and ossicular discontinuity in two representative temporal bone experiments that were part of the development phase of this chapter. Measurements were made with both the HARP system (solid) and the Mimosa system (dashed) in the same temporal bone.
5.3.3.2 Mean Results
Figure 5.10 shows the mean differences (thick lines) between the HARP and Mimosa PR measurements for all four of the development phase experiments, as well as individual differences (thin lines). Overall, PR measured by the HARP device is larger than Mimosa measurements at low frequencies (below 600-700 Hz) and smaller at high frequencies (between 2 and 6 kHz, the limit of the Mimosa measurements). The differences at low frequencies are smaller for the two fixation states compared to the initial state and the disarticulation state.

Figure 5.10 (A-D): Comparison of the HARP and Mimosa systems. Mean (thick lines) and individual (thin lines) differences between HARP and Mimosa measurements for initial, malleus fixation, stapes fixation, and ossicular discontinuity for the four development phase experiments.
5.3.3.3 Statistical Analyses of Mimosa and HARP Comparisons

Figure 5.9 & 5.10 show higher HARP PR in the low frequencies, and lower HARP I in the higher frequencies, when compared to Mimosa. We averaged the PR measured for each manipulation state over a low frequency range (200 to 500 Hz), and a “high frequency” range (the high frequency range of the Mimosa device, 3500 to 5500 kHz) in order to statistically compare (via t tests) the HARP Mimosa PR results (n=4). For low frequency data, significant differences only occur between HARP and Mimosa PR means in the initial normal state (p=0.01). Observed frequency differences between HARP and Mimosa data at low frequencies (the higher PR for HARP measurements) were not statistically distinguishable in fixed states, as fixation causes increases in PR, up to near the upper limit (~1), especially for the HARP measurements. For high frequency (3500 to 5500 kHz) comparisons, no significant differences occurred, despite the observed trend of higher PR in the Mimosa measurements. This may be due to the wide variation in the data at these frequencies.

5.4 DISCUSSION

5.4.1 Frequency-Domain Reflectance

Frequency-domain PR obtained with the HARP device (n=5) show similar results to previous reports (in this work and others) for similar frequency ranges (as clearly shown by Figure 5.6 which compares these results with results from Chapter 4). This demonstrates that various systems and methodology can produce similar PR results. Both stapes and malleus fixation result in increases in PR around 400-800 Hz, while ossicular discontinuity results in decreases in PR in a similar frequency range, generally presenting as a sharp notch in the PR between 600 and 900 Hz. These differences are consistent with increases in stiffness due to fixation, and the introduction of a resonance due to disarticulation due to a decrease in damping and an increase in compliance.
We found significant differences in PR at low frequencies (400-1000 Hz) between initial measurements and both malleus fixation (p=0.0403) and disarticulation (p=0.0209), but not between initial and stapes fixation (p=0.0945). Significant differences were also found between disarticulation and both malleus (p=0.0001) and stapes (p=0.0004) fixation. As expected, no significant differences were found between the normal and the reversed malleus fixation (near normal) measurements. It should be noted that no significant differences were found between stapes and malleus fixation in any frequency range. As previously explained in this work, separating pathology from normal is of decreased diagnostic value, as the audiogram readily separates those with normal hearing from those with conductive hearing loss. This data would support the use of reflectance to separate disarticulation from fixation, but frequency-domain analysis of reflectance measurements alone could not differentiate malleus fixation from stapes fixation. This is why prior diagnostic techniques reported in this work have combined this information with audiometric information.

When compared to Mimosa data with more limited frequency ranges (200-6000Hz), the extended frequency range of the HARP device (up to 20 kHz) does not add significant diagnostic information in the frequency domain, as the most significant observable changes occur at frequencies below 1 kHz.

5.4.2 Time-Domain Reflectance

Time-domain reflectance data analyses require high-frequency measurements, which can be obtained by the HARP system. The TDR results demonstrate systematic effects due to simulated middle-ear pathologies. Figure 5.8 shows the TDR changes from normal. All manipulation states have similar TDR from time zero to 0.075ms. At longer time intervals, TDRs increase in both malleus fixation and stapes fixation, with the malleus fixation changes being larger and earlier in time. Ossicular discontinuity results in a short latency (0.2 ms) decrease in TDR followed by an increase in TDR. The first major separation between pathologies that we notice in time is an increase in malleus fixation TDR just below 0.2ms. The next
notable change is in disarticulation, where we see decreases in TDR just above 0.2ms. Just after that, we see increases in TDR for stapes fixation, near 0.25ms, although this increase is smaller than the observed increase due to malleus fixation.

The round-trip delay through the human middle ear is estimated to be around 0.2 ms (Puria 2003). If we consider this round trip middle-ear delay, combined with the delay caused by the ear-canal (which can be estimated from the location of the first peak, which is approximately 0.075ms in our preparation) these changes in TDR occur at times consistent with these delays. Additionally, these timing changes are consistent with middle-ear anatomy. We would expect earlier pathology-induced differences for manipulations closer to the TM; if we focus on the time when the manipulation begins to effect TDR (t>0.1ms), the malleus fixation is closest to the measurement location and exhibits the earliest difference (an increase in TDR), the incudostapedial joint is the next closest manipulation location and shows a decrease in TDR at an intermediate time, and the footplate of the stapes where the stapes fixation occurs is the farthest from the TM and shows an increase in TDR last in time, right after the decrease due to ossicular discontinuity.

The magnitude and direction of these changes are also consistent; increases in TDR for both fixations, with malleus fixation exhibiting larger increases, possibly due to the lack of the incudomalleolar and incudostapedial joint which allows for increased motion even with a stapes fixation (and similar to larger increases observed for malleus fixation as compared to stapes fixation in published umbo velocity measurements from Nakajima et al 2005), and decreases in TDR for disarticulation. Thus, these changes in time, and the magnitude direction of these changes are also consistent with the anatomy and associated delays of individual structures. However, these changes could also be explained by changes in the resonance of the TM due to manipulation. If the resonance, or best frequency, of the system shifts due to manipulation, the period of a given measurement would also shift (inversely, as the period (T)=1/frequency(f)). It is therefore possible that the timing
differences in the three manipulations could be the result of differences in the resonance of the TM in the different manipulation states.

There are statistically significant differences in mean $TDR$ between the disarticulation condition and all others. The mean $TDR$ change from normal between stapes and malleus fixation showed significant differences as well. This is the only reported significant difference found between malleus and stapes fixation using reflectance measurements alone. While we observe these significant differences in a very controlled temporal bone preparation, these changes are small, and it is possible that while statistically significant, these tenth of a millisecond differences would be difficult to distinguish in a clinical setting when comparing an individual measurement to population averages given the large variations in normal populations. The exploration of $TDR$ measurements in clinical populations may provide insight as to whether these significant differences could be clinically useful. In addition, the additional information in both the frequency and time domain gained from these high-frequency reflectance measurements may prove diagnostically useful by incorporation with various analytical techniques, one of which will be explored in the next chapter.

### 5.4.3 Comparison of HARP & Mimosa Measurements

Not only did making HARP and Mimosa measurements in the same preparations help in the development phase for this work where we worked out the algorithms necessary for the calculation of reflectance, but it also provided an opportunity to compare these two systems. Direct comparisons in the frequency domain of measurements taken with the HARP system and the Mimosa system in the same preparations show good agreement, although there are consistent differences between the two techniques. The HARP PRs are consistently larger at low frequencies ($< 1$ kHz) and smaller at higher frequencies, although significant differences only occur in the low frequency range (200-500 Hz) in the initial normal condition. One likely source of these differences is in the choice of the characteristic ear-canal impedance needed to compute the reflectance. Reflectance is sensitive to
the value used for the characteristic impedance. The Mimosa system uses an average ear canal area to estimate characteristic impedance in each ear, while the HARP system's surge impedance provides an estimate of the cross-section at the measurement location in the canal for each individual ear. At frequencies above 3 kHz, the HARP results in PR that is lower than the Mimosa. The Mimosa PR frequently exceeds 1, supporting the increased accuracy of the HARP system. It is possible that these differences are due to the differences in the sound source and microphone (such as reduced cross-talk), which could also result in more accurate HARP measurements at frequencies above 3kHz.

5.6 CONCLUSIONS
This work served as a novel exploration of high-frequency reflectance measurements of pathology analyzed in the frequency and time-domain. We give a detailed account of the development of the technique with experimental support of its validity. We make reflectance measurements at frequencies as high as 20 kHz in temporal bone preparations that have manipulations to simulate pathology. The extended frequency range provides the adequate temporal resolution necessary for time-domain analyses. We also make direct comparisons of our high-frequency system (HARP) and a commonly used FDA approved reflectance system (Mimosa) used in the previous chapters of this dissertation. When comparing the two in the frequency domain, the extended frequency range of the HARP data does not add significant diagnostic information. HARP and Mimosa results show good agreement overall, although there do appear to be some consistent differences at the low frequencies as well as above 3 kHz. Time-domain reflectance results exhibit consistent changes due to pathology with some significant differences that may be explained by differences in the time delay between affected structures that are anatomically closer versus farther from the TM, but the clinical utility of these differences is unknown.
5.6 REFERENCES

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Feeney et al. (2013) Consensus statement: Eriksholm workshop on wideband absorbance measures of the middle ear. Ear Hear, 34, 78S-79S.
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Chapter 6

Exploration of Computational Modeling with Potential Implications for Diagnostic Use

_The content of this chapter represent a manuscript that is being prepared for publication. I have played a major role in all aspects of this work._

6.1 INTRODUCTION

Previous chapters in this thesis have shown how reflectance can be used as a non-invasive method to aid in the diagnosis of pathology. Differences in $PR$ are found between fixations and disarticulations, characteristic patterns in $PR$ have been shown in patients with superior semicircular canal dehiscence, and it has been demonstrated that combining reflectance data with audiometric data increases the ability to differentiate malleus and stapes fixation. This work has been based on results from clinical patient data and temporal bone preparations with simulated pathology. The novel exploration of high frequency and time domain reflectance ($TDR$) in Chapter 5 evaluated this methodology, assessed the additional information provided by these approaches, and led to observations of small pathology related differences in the $TDR$ that appear consistent with theories of spatial separation of ossicular delay. Despite this observation, the magnitudes of the pathology-related differences were small and the individual variability too large to provide any direct diagnostic value. The work presented in this chapter uses a preliminary model-based analysis to explore whether the high frequency reflectance measurements provide any advantage in understanding the effects of pathology on $PR$.

We investigate a novel external-ear model coupled to several simple middle-ear models designed to describe the transmission of sound power through the external ear and power absorbance by the middle and inner ear. The ear-canal has largely been ignored when it comes to reflectance measurements for multiple reasons: (a)
Simple uniform-tube models of the ear canal suggest the canal has little effect on the measured $PR$; (b) it has been shown that $PR$ is relatively unaffected by variations in measurement location in the canal (Huang et al 2000; Voss et al 2008). However, measurements of reflectance in different ear canal locations do differ, and theoretical analyses have shown that significant difference can occur throughout the frequency range due to spatial variations in the shape of the canal (Farmer, Fedor & Rabbit 2002).

We hypothesize that there are effects of the ear canal on reflectance measurements, that these effects are due to non-uniformities in the ear canal, which are typically ignored in other models, and that these effects are more significant at higher frequencies where the wavelengths of sound start to approximate the scale of the spatial variations in the canal. The increased prominence of these effects at high frequencies suggests that the HARP measurements will both be more susceptible to these effects and contain more information about these effects. The goal of this final chapter is to use HARP generated high frequency information with a model of both the ear canal and middle ear to separate the effects of the ear canal from the middle ear, with the idea that the isolated middle-ear components will be more clearly affected by middle ear pathology.

Given the overall goal of this work is to aid in differential diagnosis in a clinical setting, we explored a small set of simple middle-ear models with few parameters. This method has two advantages that make it more realistic for use in a clinical setting. The first is that by minimizing the number of parameters, we can use automated model fitting techniques to fit and describe the model parameters. These automated fits could be easily incorporated into clinical software and allow for patient measurements to be analyzed quickly using the modeling techniques in real time. The second advantage of this technique is that with only a few parameters, the differences in these parameters can be directly compared between the different pathological states using simple methods. With a larger set of parameters, determining which parameters are systemically affected by pathology could prove
more complicated and more challenging.

6.2 METHODS

This model exploration uses the data collected in the five HARP experiments from Chapter 5. The methods for collecting this data are explained in great detail in the previous chapter. Here we focus only on the specifics of our modeling technique.

We model the ear canal as seven concatenated conical sections terminated by an overly-simplified middle-ear model. The lengths of the conical sections in the ear-canal model are always $1/7$ of the total length of the concatenated sections. The total length is fixed by the one-way travel time (a fitted parameter initially based on the TDR) multiplied by the speed of sound. These lengths are consistent across manipulation states in each individual bone. The diameter of each conical section, however, is a fitted parameter that can vary, and this results in 8 fitted parameters that represent the diameters of the sections in the ear-canal model. As the diameter of the ear canal varies along its length, the hypothesis is that variations in diameter will result in an ear-canal model that is more realistic than a simple tube model. We explore three different terminating middle-ear models: a series RC circuit, a series RLC circuit, and a series RLC circuit in parallel with a series RC circuit. Each circuit element adds a single parameter that can vary in our model fits.

Our model is fit to our data by minimizing the mean-squared difference between the model and the impedance and reflectance measurements at several selected frequencies. The fit parameter values are determined as the value at which the model and experimental data converge. This fitting technique results in an error value that is based on the deviation between the model results and measurements. The fit is based on four different variables: (1) normalized impedance magnitude (dB), (2) impedance phase, (3) reflectance magnitude (dB), and (4) PR. The frequencies selected include 1 kHz plus 9 linearly spaced frequencies below 1 kHz (with 0.1 kHz intervals) plus 21 logarithmically spaced frequencies above 1 kHz.
(with 1/6 octave intervals). The lowest frequency is 0.1 kHz and the highest frequency is 11.3 kHz. The same frequencies are used for every model fit.

Our measurements in which the foam probe tips are glued into the same preparation across a set of manipulations provide a test of the model in that the model components related to the ear canal should be relatively unaffected by the middle-ear manipulations. While comparison of the effect of pathology on the 'ear-canal' parameters would not be easily performed in a clinical test population, we can explore how these diameters vary between manipulations in our temporal bone preparation. We therefore use two methods with regard to ear-canal diameter parameters. The first method allows the automated fit to vary the ear-canal diameters from one manipulation to another (i.e. the value of the ear-canal diameter of any one conical section set can differ between the initial measurement, the malleus fixation measurement, the reversal measurement, etc.). The second method fixes the diameters of the seven conical sections in all of the manipulation analyses with the fit to the initial normal state. Thus, we have 6 total model states that we are exploring:

Table 6.1: Model Variation Combinations for R, L, and C's middle-ear circuit parameter values as well as in Ear-Canal Parameters (ECPs)

|           | RC                     | RLC                        | R1LC1||R2C2 |
|-----------|------------------------|----------------------------|----------|
| **Vary ECP** | 1) $R_1$, $C_1$ & ECPs vary | 2) $R_1$, $L$, $C_1$ & ECPs vary | 3) $R_1$, $C_1$, $L$, $R_2$, $C_2$ & ECPs vary |
| **Fix ECP**  | 4) $R_1$ & $C_1$ vary   | 5) $R_1$, $L$, & $C_1$ vary | 6) $R_1$, $C_1$, $L$, $R_2$, & $C_2$ vary |

The model fits produce two categories of information: 1) the fitted-parameter values for the middle-ear and ear-canal elements (the ear-canal elements are only used for the three models in which these ear-canal parameters can vary across manipulation), and 2) an error value which represents a “goodness of fit” for each
individual fit. We have five experiments, each with five manipulation states (initial, malleus fixation, reversal, stapes fixation, and disarticulation). Thus, for each of the six model states as described in Table 6.1, we fit 25 pieces of data.

6.3 RESULTS

6.3.1 Sample Model Fit

Figure 6.1 shows a sample model fit to disarticulation data from a single experiment, grm030, using the RLC model with the ear-canal parameters fixed. Experimental data is shown in blue, and model fits are shown in red. The top row displays the normalized impedance (dB), $R$ (dB), and $TDR$ (kHz), respectively, and the bottom row displays the impedance phase, and $PR$. While some fine structure in the data is not fit by the model, such as high frequency $PR$, the model fits capture many features of the experimental data.

Figure 6.1: Example of model fits for grm030 disarticulation state with the RLC model where the ear-canal diameters were fixed across manipulations. Experimental data is shown in blue and model data in red. The top row displays the normalized impedance (dB), reflectance (dB), and $TDR$ (kHz), and the bottom row displays the impedance phase, and power reflectance.
6.3.2 Variability in Ear-Canal Parameters Across Manipulation

The variability in the ear-canal diameter within a single conical section was assessed by comparing the diameters fit to each manipulation to the diameters fit to the initial normal state. We computed the absolute value of the percentage change from the initial fit for each diameter and then averaged those percent changes across all manipulation states in a single preparation. This procedure was repeated for each of the three model conditions where the diameters varied (model 1, 2, and 3 from Table 6.1) and the results are shown in Table 6.2. Of the three terminating middle-ear models we explored, the series RLC circuit model results in the least variability in the ear-canal diameters across manipulation states, with the series RLC circuit in parallel with a series RC circuit resulting in the greatest amount of variability in these parameter values. The results from the series RC circuit are only slightly larger than those from the series RLC circuit. However, even the series RLC circuit model leads to an average variation in the ear-canal parameters of 30%.

These variations point out that the model-fit procedure allows manipulation-induced changes in the measurements to modify the ear-canal parameter values. This is inconsistent with our goal of using the model to separate out the effects of the ear canal and middle ear. This lack of independence led us to investigate data fits when the ear canal parameters were fixed by the initial state measurements.

Table 6.2: Variability in Ear-Canal Parameters Across Manipulation

|        | RC    | RLC   | RLC || RC |
|--------|-------|-------|------|-----|
| grm037 | 30.83%| 23.21%| 25.25%|
| grm034 | 25.63%| 31.00%| 49.35%|
| grm032 | 34.63%| 31.00%| 42.67%|
| grm031 | 35.76%| 35.76%| 74.73%|
| grm030 | 41.03%| 29.36%| 40.43%|
| Average| 33.58%| 30.07%| 46.48%|
| STD    | 5.14% | 4.04% | 16.18%|

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6.3.3 Error Values Based on 'Goodness of Fits'

Table 6.3 and 6.4 show details of the errors produced by our model fits. These scaled error values are unitless and thus the significance of the absolute value was determined by comparing error values to the root-mean-square (RMS) differences between model and experimental data. For example, the RLC fit to the disarticulation state for all frequencies in Figure 6.1 results in an error value of 245 and RMS differences in impedance magnitude of 3.74 (dB), in impedance phase of 0.17 cycles, and in PR of 0.24. If we consider only frequencies below 6 kHz, the RLC fit to the disarticulation state in Figure 6.1 results in RMS differences in impedance magnitude of 0.93 (dB), in impedance phase of 0.03 cycles, and in PR of 0.14.

Alternatively, instead of focusing on the absolute values of these errors, since we are comparing these model conditions with each other, we can instead compare the error values for one model condition against another. These relative error values provide an indication as to whether one model condition produces better results than another. Table 6.3 shows errors for all of the fit data, and these error fits are averaged in Table 6.4. These error values point out that all six of the model states have the most difficulty with modeling the disarticulation state. The errors are smaller for the three model states that allow the ear-canal diameters to vary when compared to the same middle-ear model with fixed ear-canal diameters. The error values also tend to be smallest for the most complicated middle ear model (the RLC||RC) and largest for the RLC model.
Table 6.3: Detailed Errors in Model Fit Data

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6.3.4 Middle-Ear Parameters

Each model fit produces a value for each circuit element included in the middle-ear model. We explored how these 2 to 5 elements (depending on model condition) varied as a result of manipulation. Systematic variations as a result of manipulation state were found consistently for the first series RC elements of each model condition. There were no systematic variations found in the mass in the series RLC circuits, or in the series RC elements that were in parallel with the series RLC branch of the RLC||RC circuit. Thus, we focused our analyses on the RC elements of the circuit (or in the case of the RLC||RC model condition, on the RC elements from the RLC branch of this circuit model, which we call R₁ and C₁).

Figure 6.2 shows two-dimensional plots of the values for the resistive (R, damping) and stiffness (K, or 1/C) elements for each of the six model conditions. All panels on the left hand side are for the conditions in which we allowed the ear-canal diameters to vary with each measurement condition, and all panels on the right side show the results when the ear-canal diameters were fixed to the values predicted by the fit to the initial normal state. All parameter values were normalized by the characteristic impedance. Regardless of model condition, the normal and malleus reversal data points are essentially indistinguishable, consistent with the reversal returning the middle ear to its normal state. The three simulated pathology states, however, are separated in this two-dimensional figure for each of the six model conditions, although the "area" which each pathological state covers for a given condition does varies between conditions.
Figure 6.2: Model parameter values for the resistive element (R; plotted on the horizontal scale) and the stiffness element (K; plotted on the vertical scale) normalized by the characteristic impedance. Each panel includes data from a single model condition used to analyze measurements in 5 bones. The fitted parameters for each of the 5 bones are separated by color into: initial measurements, malleus fixation, reversal of malleus fixation, stapes fixation, and disarticulation of the incudostapeidal joint. All panels on the left hand side are for the conditions in which we allowed the ear-canal diameters to vary, and all panels on the right side show the results when the ear-canal diameters were fixed.
The disarticulation state consistently produced lower values of stiffness (K) when compared to the two fixation states. The malleus and stapes fixation show K values that are similar to each other but the malleus fixation consistently shows increased values for the damping (R) parameter. Individual one-way ANOVAs on the stiffness (K) values found significant differences between disarticulation and both stapes and malleus fixation for all model conditions. Individual one-way ANOVAs on the damping parameter values found significant differences between malleus fixation and both stapes fixation and disarticulation for all six model conditions. Thus, combining the stiffness and damping parameter fit values on two-dimensional plots can separate out the three pathologies. This analysis separated malleus and stapes fixation, two pathologies that are often difficult to distinguish, using only reflectance information (something that has not been done previously); this separation occurred because of differences in the fitted R values, even though the range of fitted K values were similar in the two conditions.

6.4 DISCUSSION

We modeled high frequency reflectance with three simple middle-ear models coupled to a moderately complex ear-canal model that allows non-uniformities within the ear canal. We explored two variations of the ear-canal model (where the diameter of each section was allowed to either vary across manipulation states or was fixed after the initial state) coupled to three different terminating middle-ear models (RC, RLC, and RLC||RC circuits) in order to determine which model provided the best model fits to our data with the least number of parameters, as well as which model proved to be the most clinically useful. These analyses utilized our HARP data from Chapter 5 because the ear-canal model fits depend upon high-frequency reflectance and impedance information.

6.4.1 Middle-Ear Parameters

Regardless of which model is fit to our HARP data, the parameter values for the stiffness and damping elements (which in the case of the RLC||RC circuit are the R
and C from the RLC branch, which are called $R_1$ and $C_1$ as opposed to $R_2$ and $C_2$ from the parallel RC branch) of the middle and inner ear vary consistently with manipulation across our five experiments. The model parameters of other circuit elements did not show consistent systematic variation as a result of pathology. One possible explanation for this is that these two particular stiffness and damping elements ($R$ and $C$) may account for much of the resistance and reactance at the eardrum at low frequencies below resonance, where the manipulations produce the largest changes in the middle-ear impedance. Most of the reflectance related changes we observe are in a lower frequency range below the resonance (as demonstrated in all chapters of this work), where stiffness dominates the reactance. If the stiffness is dominating the reactance in the frequency range where the changes are occurring, this may explain why the stiffness element of these models is what results in substantial changes, regardless of which model condition we consider.

Consistent with simple models of the ear, the fits suggest that malleus and stapes fixation increase the stiffness of the ear, while ossicular disarticulation reduces stiffness. The fitted parameters also suggest significant manipulation-induced variations in middle-ear damping; the damping is lowest in the disarticulated state (consistent with the removal of cochlear damping) and highest after malleus fixation. This increase in damping due to malleus fixation may be explained by malleus fixation causing a reduction in the number of parallel 'shunt' paths in the middle ear (i.e. removing the cochlea, the incudostapedial joint, and the incudomalleolar joint), thereby forcing all motion through a highly damped TM shunt impedance. Figure 6.3 shows a schematic relating to this hypothesis. If the impedances are dominated by damping ($R$), fixing the stapes (i.e. removing $R_c$) results in one less parallel pathway than in the normal condition, which would result in increases in the overall damping. We observe increases in the damping parameter $R$ for stapes fixation as compared to normal. By fixing the malleus, both the parallel pathway from the incudostapedial joint as well as the incudomalleolar joint are removed, further increasing the total damping. Regardless of the
mechanism, the data shown in Figure 6.2 are the first demonstration of a technique to separate malleus and stapes fixation based solely on reflectance measurements.

![Diagram of ear canal components](attachment:diagram.png)

Figure 6.3: Possible explanation for differences in damping (R) parameter values between stapes and malleus fixation. Damping subscripts are as follows: uncoupled TM (TMU), TM and malleus (TMM), incudomalleolar joint (IMJ), incus (INC), ISJ (incudostapedial joint), and cochlea and stapes (CS).

### 6.4.2 Variability in Ear-Canal Diameters

The external ear parameters were designed to fix the contribution of the ear canal in order to separate out effects on reflectance on the ear canal from effects on the middle ear. Theoretically, if our model was working perfectly, the ear-canal diameter fits would be consistent in a single preparation across manipulation state, as the foam tips were glued into the canals and the position of each tip did not change between different manipulations. However, the model-fitting procedure led to significant variations in the ear-canal parameters. Table 6.2 shows that there is substantial variability in these diameter fits. The RLC||RC model resulted in the largest variability in the ear-canal diameters. The RLC and RC models result in the less variability in the ear-canal diameters, but the variability is still 30% or greater from the initial normal state fits.
These results suggest that the ear-canal and middle-ear parameters are not completely separable. However, estimates of the middle-ear parameters show similar behavior when the fitting procedure either fixed the ear-canal diameters or allowed its dimensions to vary with measurement condition, which suggests that the fit parameter values in the middle-ear may not be significantly sensitive to changes less than 47% in the ear-canal diameters. We are able to fit these diameters to the normal values and force them to stay consistent across manipulation state, effectively removing this variability. However, the results show that regardless of whether the ear-canal diameters are fixed or vary, the middle-ear model parameter fits still provide significant separation between pathology. This is advantageous in that in a clinical setting, we would not have the ability to force these ear-canal parameters to fits from a “normal” state, so the fact that the model still produces separation between pathology is useful.

### 6.4.3 Goodness of Fit Based on Errors

We evaluated our models based on error values that represented a goodness-of-fit of our model results to our data. These errors are based on the deviation between the model and measurements. The relative errors that represent the goodness of the fits of our model to our data do show some consistent patterns that are model dependent. Overall, the errors are smaller for the three conditions where we allow the ear-canal diameters to vary as well as for the model conditions that contain middle-ear models with more parameters. The RLC||RC model results in the smallest error values. However, while the RLC||RC model condition provided the best fits, the parameter values that resulted from this model were the most inconsistent. Table 6.2 shows that the ear-canal diameter fits show three times the standard deviation of variability as compared to the other to models. In addition, some of the parameter values resulting from this model condition seemed inaccurate as they were either significantly larger or smaller than the range of values that were occurring for these parameters in other manipulation states within the same preparation (i.e. values of 1 or 50000 when most absolute values were around 2000). The automated model fitting procedure is limited in the number of
parameters it can fit, and it is possible that this model condition had too many parameters and that these odd results had some inaccuracies due the limitations in this automated fitting procedure.

### 6.4.4 Model Comparisons

As to which of the three terminating middle-ear models does the best job, the results are somewhat inconclusive. Across all models, the R and C (or R₁ and C₁ in the R₁LC₁||R₂C₂ model) parameters seem to be the most crucial with regard to differentiating pathology. The RLC||RC model produces the best fits (suggested by the smallest error values) whether you vary the ear-canal diameters or not, but also resulted in the largest variations in ear-canal section diameters when they were allowed to vary. Adding a mass (or L) element in the RLC model as compared to the RC model resulted in slightly better fits when the ear-canal parameters varied, but the RC model had better fits than the RLC when the diameters were fixed. The RLC model had slightly smaller variations in ear-canal diameters across manipulation as well, but overall, the results from the two models seem comparable and one does not consistently perform better than the other. Perhaps the lack of benefit from adding a mass element is due to the fact that reflectance changes caused by manipulation occur in a stiffness dominated frequency region, and have little effect on the mass. It should also be noted that while the RLC||RC model condition produces the best fits, it also produces some atypical results, which we have already suggested may be due to the fact that this model requires our automated fitting procedure to fit too many parameters.

### 6.5 CONCLUSION

Overall, this work shows that automated model fitting techniques of HARP reflectance data allows for separation of different conductive pathological conditions in a procedure that could be easily implemented into clinical software. Significant differences in two middle-ear model parameters, damping (R) and stiffness (K), allowed for separation of all three pathologies. Malleus and stapes
fixation were consistently significantly different from disarticulation with regards to the stiffness parameter, and stapes fixation and malleus fixation were consistently significantly different with respect to the damping parameter. The significant difference in the damping parameter between malleus fixation and stapes fixation is notable as no other reflectance analyses has been able to differentiate these two pathologies without the use of additional information (such as the air-bone gap).

This separation based on the \(R\) and \(K\) parameter values is robust and is consistent regardless of whether we allow the ear-canal diameters to vary across manipulation state or which terminating middle ear model we use. Additional work needs to be completed in order to better understand how this model is working and why, but the robust effect we find in separating pathology suggests that high-frequency reflectance measurements can provide separation between malleus fixation, stapes fixation, and disarticulation with reflectance information alone. Exploring this model using high-frequency reflectance measurements in patients would be a next step in determining the clinical utility of this technique.

6.6 REFERENCES


Chapter 7

Conclusions, Proposed Experiments, and Future Directions

7.1 Overview

The causes of conductive hearing loss are often difficult to determine despite the frequent presentation of patients with various middle-ear diseases in the clinic (Merchant et al., 1998). Current clinical practice falls short in the differential diagnosis of patients with conductive hearing loss, an intact tympanic membrane, and a well-aerated middle ear. This work served as a comprehensive evaluation of the diagnostic utility power reflectance on the differential diagnosis of pathology. Reflectance and velocity measurements using laser-Doppler vibrometry were made in normal subjects (Chapter 2), in clinical patient populations (Chapters 2 & 3), and in temporal bone preparations that simulated pathology (Chapters 4 & 5). Diagnostic techniques were explored using reflectance measurements to differentiate various conductive pathologies, to preoperatively screen for superior semicircular canal dehiscence (SCD) in patients with and without conductive hearing loss, to track mechanical changes pre and postoperatively in patients with SCD, and to differentiate patients and temporal bones with partial or complete ossicular discontinuities (Chapter 3). Novel high-frequency reflectance measurements were also made in temporal bone preparations which simulated conductive pathologies and were analyzed in both the frequency and time-domains, and modeling techniques utilizing these high frequency measurements were used to differentiate conductive pathologies using only reflectance measurements, showing the ability to differentiate stapes and malleus fixation for the first time (Chapters 5 & 6).
7.2 Power Reflectance and Umbo Velocity Measurement in Patients

Power reflectance (PR) measurements have shown promise as a presurgical differential diagnostic of conductive hearing loss. Chapter 2 systematically explored PR, as well as umbo velocity (UV) measurements, in a strict normal population and compared these measurements to measurements made in patients with conductive hearing loss that was determined to be caused by either stapes fixation, ossicular discontinuity, or superior semicircular canal dehiscence. The frequency dependence of the PR measurements was different for the three pathologies: stapes fixation resulted in small increase from normal at low-to-mid-frequencies, while large narrowband decreases from normal were seen for ossicular discontinuity (between 500 and 800 Hz) and SCD (<1 kHz).

7.3 Using Reflectance as a Diagnostic Tool

In patients with conductive hearing loss, the loss is most commonly due to fixation of the stapes, ossicular discontinuity, or a third window lesion of the inner ear such as SCD. Currently, there are no diagnostic tests that can reliably differentiate between the pathologic conditions responsible for conductive hearing loss. A diagnostic test that differentiates among these disorders and that can be used in an office setting would be of clinical value. Chapter 3 demonstrated that PR measurements could aid in the differential diagnosis of pathologies causing conductive hearing loss preoperatively. Our results showed that the frequency dependence of the PR measurements was different for the three pathologies, and that PR measurements combined with audiometry showed high sensitivity and specificity as a clinical diagnostic tool in the differential diagnosis of these disorders.

While differentially diagnosing conductive pathologies is of great interest, the diagnosis of SCD regardless of whether there is a CHL present is also a diagnostic challenge, as is tracking patients who have had surgical management of SCD who may have residual symptoms. Chapter 3 provided evidence that PR in conjunction
with a new algorithm to detect certain features in $PR$ response could be used to screen patients for SCD in the early stages of a diagnostic workup. Power reflectance can aid in the early stages of diagnostic workup to enable earlier diagnosis and prevent unnecessary treatment. This chapter also showed that $PR$ has the potential to be a useful tool in not only diagnosing but also in tracking patients with SCD pre and postoperatively, particularly in patients who may have recurring symptoms. Power reflectance measurements were sensitive to mechanical changes resulting from surgical management of SCD. Overall, our postoperative patient population showed "normalized" $PR$ results when compared to preoperative data. Further studies including larger sample sizes of patients with recurring symptoms would be crucial in determining how $PR$ can be used. Additionally, comparing surgical techniques such as plugging versus resurfacing will also be useful.

Another diagnostic challenge is differentiating partial ossicular discontinuity versus complete ossicular discontinuity. Chapter 3 also showed that when a CHL that is larger at higher frequencies is present, partial discontinuity should be strongly considered as a possible cause. Combining this audiometric information with a mechanical measurement such as $PR$, which appears equally sensitive to discontinuities of varied strength, may be able to provide confirmation of a suspected partial disarticulation in someone with a high-frequency CHL. These results were supported by experimental findings in a well-controlled temporal-bone preparation.

### 7.4 Controlled Exploration of Reflectance in Temporal Bones

Given the intersubject variability seen in both $R$ and $UV$ in normal, healthy subjects, knowledge of how the healthy normal ear responds, and then subsequently changes as a result of the development of a specific pathology, provides the most controlled assessment of how these measurements are affected by pathology. Chapter 4 investigated the effects of pathologies such as those discussed in Chapters 2 and 3 in a controlled and systematic way. We reported measurements human cadaveric
temporal bone simulations of stapes fixation (n=8), malleus fixation (n=10),
ossicular discontinuity (n=10), and SCD (n=8). These results were consistent with
previous studies and were also strikingly similar to patient data. Given the level of
control that we were able to obtain in these studies (as opposed to in clinical data),
these results strongly support the clinical data findings and suggest that any
uncontrolled variables did not significantly impact our results.

7.5 Novel High-Frequency Reflectance Analyzed in the Frequency
and Time Domains

Due to frequency limitations in commercially available devices (which were used in
the first four chapters of this work), wideband acoustic immittance (WAI) and PR
have not been well described at frequencies above 6-8 kHz. Additionally, analyses of
these measurements up to this point have focused on the responses to stimulus
frequencies below 3-4 kHz, while ignoring high-frequency or time-domain
information. A recent report from the Eriksholm Workshop on Wideband
Absorbance Measures of the Middle Ear emphasized the need for these types of
measurements and analyses and stated that “Although the pressure reflectance
phase has been reported in a number of early articles, there was consensus that the
value of the temporal characteristics of WAI measurements has largely been
ignored” (Feeney et al. 2013). In an effort to address this question, Chapter 5 used a
novel approach to measure PR that utilized high-frequency signals and analyzed
reflectance in both the frequency and the time domains (time-domain reflectance,
TDR). We give a detailed account of the development of this novel technique with
experimental support of its validity. We made reflectance measurements at
frequencies as high as 20 kHz in temporal bone preparations that had manipulations
to simulate pathology. The extended frequency range provided the adequate
temporal resolution necessary for time domain analyses. We also made direct
comparisons of our high-frequency system (HARP) and a commonly used FDA
approved reflectance system (Mimosa) used in the previous chapters of this
dissertation. When comparing the two in the frequency domain, the extended
frequency range of the HARP data did not add significant diagnostic information. HARP and Mimosa results showed good agreement overall, although there did appear to be some consistent differences at the low frequencies as well as above 3 kHz. Time-domain reflectance results exhibited consistent changes due to pathology with some significant differences that may be explained by differences in the time delay between affected structures that are anatomically closer versus farther from the TM, but the clinical utility of these differences is unknown. The exploration of TDR measurements in clinical populations may provide insight as to whether these significant differences could be clinically useful.

7.6 Exploration of Computational Modeling of High-Frequency Reflectance with Potential Implications for Diagnostic Use

The magnitudes of the pathology-related differences in TDR were small and the individual variability too large to provide any direct diagnostic value. We used a preliminary model-based analysis to explore whether the high frequency reflectance measurements provide any advantage in understanding the effects of pathology on PR. We investigated a novel external-ear model coupled to several simple middle-ear models designed to describe the transmission of sound power through the external ear and power absorbance by the middle and inner ear. Overall, this work showed that automated model fitting techniques of HARP reflectance data allows for separation of different conductive pathological conditions in a procedure that could be easily implemented into clinical software. Significant differences in two middle-ear model parameters, damping (R) and stiffness (K), allowed for separation of all three pathologies. Malleus and stapes fixation were consistently significantly different from disarticulation with regards to the stiffness parameter, and stapes fixation and malleus fixation were consistently significantly different with respect to the damping parameter. The significant difference in the damping parameter between malleus fixation and stapes fixation is notable as no other reflectance analyses has been able to differentiate these two pathologies without the use of additional information (such as the air-bone gap). Additional work needs to be
completed in order to better understand how this model is working and why, but
the robust effect we find in separating pathology suggests that high-frequency
reflectance measurements can provide separation between malleus fixation, stapes
fixation, and disarticulation with reflectance information alone. Exploring this
model using high-frequency reflectance measurements in patients would be a next
step in determining the clinical utility of this technique.