

ABSTRACT

Title of Document: THE IMPACT OF RHEUMATOID ARTHRITIS ON MIDDLE EAR FUNCTION.

Caroline Marie Roberts,
Doctor of Clinical Audiology (Au.D.), 2007

Directed By: Assistant Professor, Tracy Fitzgerald, Ph.D.,
Department of Hearing and Speech Sciences

Rheumatoid arthritis (RA) is an autoimmune disease that causes inflammation and swelling of the joints. Middle ear joints may be subject to rheumatic involvement similar to other joints in the body. Results from previous studies examining audiological characteristics in individuals with RA have varied with respect to incidence and type of hearing loss, as well as incidence and type of middle ear involvement (increased or decreased stiffness). The purpose of this study was to compare audiometric, immittance, distortion-product otoacoustic emission (DPOAE), and energy reflectance (ER) results between participants with RA and normal control (NC) participants to further examine the effects of RA on middle ear function. Twenty-one participants with RA (38 ears) were matched 1:1 based on age and gender to 21 individuals (38 ears) without RA. The following measures were completed for all participants: pure-tone air- and bone-conduction thresholds, 226-,

678- and 1000-Hz tympanograms, acoustic reflex thresholds, acoustic reflex decay, and middle ear resonant frequency. ER and DPOAEs were measured for a subset of 16 RA (28 ears) and 16 NC (28 ears) matched participants. No significant difference in prevalence of hearing loss was found between groups. Individuals with hearing loss in both groups presented with sensorineural-type hearing loss, which was typically a mild to moderate high-frequency hearing loss. No significant differences were found between groups for air- and bone-conduction thresholds. A significantly greater number of ears from the RA group had thresholds poorer than the 95th percentile for their age range and gender across the audiometric test frequencies. Generally, younger individuals with RA had poorer thresholds at 1000 and 2000 Hz compared to normative data for age and gender. No differences were found between groups for static admittance, the number of notched versus single-peaked 678- and 1000-Hz tympanograms, acoustic reflex thresholds, ER, and DPOAE measurements. The RA group had a significantly lower mean resonant frequency, consistent with an increase in the laxity or an increase in the mass dominance of the middle ear system. These significant findings revealed the importance of considering audiological assessment of individuals with RA.

THE IMPACT OF RHEUMATOID ARTHRITIS
ON MIDDLE EAR FUNCTION

By

Caroline Marie Roberts

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, College Park, in partial fulfillment
of the requirements for the degree of
Doctor of Clinical Audiology
2007

Advisory Committee:
Tracy Fitzgerald, Ph.D. Chair
Carmen C. Brewer, Ph.D. Co-Chair
Sandra Gordon-Salant, Ph.D.
Monita Chatterjee, Ph.D.
David Cooper, Ph.D.

© Copyright by
Caroline Marie Roberts
2007

Dedication

This dissertation is dedicated to those individuals who have encouraged, supported, and uplifted me through this process. I thank my husband, Chris Roberts, for his love, encouragement, and ability to help me see the light at the end of the tunnel. I thank Tracy Fitzgerald and Carmen Brewer for their support and extensive time invested in this project. Additionally, I appreciate Tracy's mentorship, guidance, and investment in my professional development throughout my academic career. And lastly, I would like to thank my classmates: Erin McAlister, Kelly King, Christine Gmitter, Lauren Wisman, and Krystal Strazik. Their collaborative support, laughter, and friendship helped guide me through not just this process but through my graduate career. They have shared in my joys and struggles, and provided strength and encouragement. And together – we can beat the Stenger!

Acknowledgements

Special thanks to Dr. Raphaela Goldbach-Mansky and Mildred Wilson for their assistance with participant recruitment at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). This research was made possible by their research efforts and acceptance of our addendum to their natural history study. Also, thanks to Carmen Brewer and Chris Zalewski for their assistance with participant supervision and report writing at the National Institute on Deafness and Other Communication Disorders (NIDCD). In addition, the contributions of the committee members are greatly appreciated: Tracy Fitzgerald, Carmen Brewer, Sandra Gordon-Salant, Monita Chatterjee, and David Cooper. Special thanks to Tracy Fitzgerald and Carmen Brewer for their tireless efforts serving as co-chairs. This research was partially funded by the MCM Fund for Student Research Excellence, from the Department of Hearing and Speech Sciences at the University of Maryland, College Park.

Table of Contents

Dedication.....	ii
Acknowledgements.....	iii
Table of Contents.....	iv
List of Tables	vii
List of Figures.....	viii
Chapter 1: Introduction.....	1
Chapter 2: Literature Review.....	4
Rheumatoid Arthritis (RA).....	4
<i>Overview</i>	4
<i>Symptoms</i>	5
<i>Etiology</i>	6
<i>Diagnoses</i>	7
<i>Pharmacological Treatment</i>	10
<i>Extra-articular manifestations</i>	11
Middle Ear.....	12
<i>Middle Ear: Anatomy</i>	12
<i>Middle Ear: Diagnostic Tests</i>	14
Wideband Reflectance.....	27
<i>Normative Values in Adults</i>	31
<i>Energy Reflectance (ER) and Middle Ear Disorders</i>	33
Rheumatoid Arthritis (RA) and the Auditory System.....	38
<i>RA and Hearing Loss</i>	38

<i>RA and Middle Ear Function</i>	48
Summary and Purpose:	55
Chapter 3: Research Questions and Hypothesis	57
Chapter 4: Methods.....	60
Participants.....	60
Procedures.....	66
<i>Audiometric Measures</i>	68
<i>Standard Immittance</i>	69
<i>Multi-frequency Tympanometry</i>	70
<i>ER and DPOAE Measures</i>	71
<i>Preliminary Data</i>	74
Statistical Analysis.....	75
Chapter 5: Results	77
<i>Preliminary Data: Location Differences</i>	77
<i>Preliminary Data: Test Order</i>	82
Audiometric Measures	82
Standard Immittance	92
Multi-frequency Tympanometry.....	100
Energy Reflectance (ER) Measures	108
DPOAE Measures	111
RA Disease Activity and Audiological Measures	113
Chapter 6: Discussion	119
Audiometric Measures	119

Standard Immittance	123
Multi-frequency Tympanometry.....	124
ER and DPOAE Measures	129
RA Demographics.....	134
Chapter 7: Conclusions	137
Appendix A.....	140
Appendix B.....	143
References.....	145

List of Tables

Table 1: Demographic and disease information for RA participants.....	63-64
Table 2: Number of participants and ears from each group included in measurements.....	67
Table 3: Comparisons of hearing loss at different threshold classifications.....	86
Table 4: Bone-conduction thresholds compared between RA and NC groups.....	90
Table 5: Air-bone gap differences compared between RA and NC groups.....	91
Table 6: Air-conduction threshold compared to age-related normative data.....	95
Table 7: 226-Hz quantitative measures compared between RA and NC groups.....	97
Table 8: Acoustic reflex thresholds compared between RA and NC groups.....	99
Table 9: Calculated admittance for 678- and 1000-Hz tympanograms compared between RA and NC groups.....	104
Table 10: Comparisons of ears within individuals in the RA group across tympanometry and pure-tone audiometry measures.....	107
Table 11: Energy reflectance (ER) measurements compared between RA and NC groups.....	112
Table 12: DPOAE level compared between RA and NC groups.....	114
Table 13: Partial correlations accounting for age and comparing RA disease involvement and audiological measures.....	115

List of Figures

Figure 1: Type A tympanogram example.....	17
Figure 2: Quantitative measures for a normal 226-Hz tympanogram.....	19
Figure 3: 1B1G tympanogram example.....	22
Figure 4: 3B1G tympanogram example.....	23
Figure 5: 3B3G tympanogram example.....	24
Figure 6: Energy reflectance (ER) “normal” example.....	29
Figure 7: Energy reflectance (ER) “abnormal” example.....	30
Figure 8: Mean energy reflectance (ER) for pilot data comparing locations.....	78
Figure 9: Mean energy reflectance (ER) ± 1 <i>SD</i> for pilot data comparing locations...	79
Figure 10: Mean energy reflectance (ER) ± 1 <i>SD</i> for pilot data comparing test- retest reliability.....	80
Figure 11: Mean energy reflectance (ER) for pilot data comparing test order.....	83
Figure 12: Mean energy reflectance (ER) ± 1 <i>SD</i> for pilot data comparing test order.....	84
Figure 13: Air-conduction thresholds compared between groups.....	89
Figure 14: Air-conduction thresholds as a function of age.....	93-94
Figure 15: 678-Hz tympanometric shape classification.....	101
Figure 16: 1000-Hz tympanometric shape classification.....	102
Figure 17: Resonant frequency compared between RA and NC groups.....	105
Figure 18: Mean energy reflectance (ER) compared between RA and NC groups...	109
Figure 19: Mean energy reflectance (ER) ± 1 <i>SD</i> compared between RA and NC groups.....	110

Figure 20: Scatterplot of air-conduction thresholds at 4000 Hz and disease duration in RA group.....	116
Figure 21: Scatterplot of air-conduction thresholds at 8000 Hz and disease duration in RA group.....	117
Figure 22: Mean energy reflectance (ER) in RA and NC groups compared to normative data.....	131
Figure 23: Mean energy reflectance (ER) in RA and NC groups compared to 95% range of normative data.....	133

Chapter 1: Introduction

Rheumatoid arthritis (RA) is an autoimmune disease which causes inflammation and swelling of the joints, and may cause the surrounding muscles, ligaments, and tendons that support the joint to become weak, loosened, or unable to function normally. The two joints located in the middle ear (incudomalleolar and incudostapedial) are freely movable joints called diarthroses; and, therefore, may be subject to rheumatic involvement similar to other joints in the body.

Multiple authors have reported a higher incidence of hearing loss in individuals with RA (28 – 60%) compared to normal controls (Heyworth & Liyanage, 1972; Kakani, Mehra, & Mehta, 1990; Kastanioudakis, Skevas, Danielidis, Tsiakou, Drosos, & Moustopoulos, 1995; Magaro et al., 1990; Özcan, Karakus, Gündüz, Tuncel, & Sahin, 2002; Öztürk et al., 2004; Salvinelli et al., 2004); however, the type of hearing loss documented has varied (Kastanioudakis et al., 1995; Magaro et al., 1990; Raut, Cullen, & Cathers, 2001; Salvinelli et al., 2004). Conductive, mixed and sensorineural hearing loss have been reported in RA populations (Copeman, 1963; Djupesland, Grønås, & Saxegaard, 1973; Gairola, Kacker, Kumar, & Malaviya, 1991; Heyworth & Liyanage, 1972; Raut et al., 2001; Salvinelli et al., 2004). The most prevalent type of hearing loss reported has been sensorineural hearing loss (Elwany, Garf, & Kamel, 1986; Kakani et al., 1990; Kastanioudakis et al., 1995; Magaro et al., 1990; Reiter, Konkle, Myers, Schimmer, & Sugar, 1980; Takatsu, Higaki, Kinoshita, Mizushima, & Koizuka, 2005). The cause of damage to the inner ear is not clearly understood, but researchers have hypothesized that the effects of the RA on middle

ear function may be associated with the greater presence of hearing loss (Elwany et al., 1986; Özcan et al., 2002; Raut et al., 2001).

In addition to a high rate of hearing loss originating in the inner ear, researchers have reported significant differences between individuals with RA and NC participants (Elwany et al., 1986; Öztürk et al., 2004; Reiter et al., 1980; Takatsu et al., 2005). Studies have reported as many as 59-70% of RA participants having abnormal middle ear function (Elwany et al., 1986; Reiter et al., 1980). Clinical immittance measures, including single- and multiple-frequency tympanometry, have indicated differences in the transmission of sound through the middle ear, including both increased stiffness (Elwany et al., 1986; Kakani et al., 1990; Öztürk et al., 2004; Reiter et al., 1980; Takatsu et al., 2005) and laxity (Moffat, Ramsden, & Rosenberg, 1977; Rosenberg, Moffat, Ramsden, Gibson, & Booth, 1978) of the middle ear system. The changes in the stiffness of the middle ear system are believed to be associated with RA involvement of the ossicular articulations (Salvinelli et al., 2004). However, these abnormalities in middle ear sound transmission do not always result in a conductive type of loss. Researchers hypothesize that some of these changes in sound transmission may be related to the increased rate of sensorineural hearing loss observed in patients with RA because the changes affect the protective mechanism of the middle ear (Öztürk et al., 2004; Salvinelli et al., 2004); however, the impact of RA on the auditory system remains the subject of debate.

Existing research on the effect of RA on the auditory system has utilized standard clinical measures of middle ear function, including tympanometry and acoustic reflex measurements, which generally focus on the transmission of lower

frequencies through the middle ear (200-2000 Hz). Energy reflectance (ER) allows evaluation of power transfer through the middle ear over a broader frequency range. This method may provide increased sensitivity to subtle changes in the efficiency of energy transfer through an auditory system affected by RA. The purpose of this research is to study the effects of RA on middle ear function in adults using multi-frequency tympanometry and ER, in addition to traditional audiometric and immittance measures.

Chapter 2: Literature Review

Rheumatoid Arthritis (RA)

Overview

RA is an inflammatory disease that affects the joints. It is an autoimmune disease that causes the white blood cells to travel to the tissue lining the joint capsules and cause inflammation. In healthy individuals, the immune system protects the body from infection and disease; however, in individuals with RA, the immune system attacks joint tissues. The tissue lining the joints, called synovium, produces synovial fluid that lubricates the joint capsules. When the synovium is inflamed, it can cause redness, swelling, stiffness, and pain around the joint (Hunder, 1999). As a result of RA, the normally thin synovium may grow into a thick, abnormal tissue called “pannus,” making the joint swollen and painful to move. As the disease progresses, the inflamed synovium can damage the cartilage and bone within the joint, and may cause the surrounding muscles, ligaments, and tendons that support the joint to become weak, loosened, or unable to function normally. This severe joint damage can begin during the first year or two that an individual has the disease (U.S. Department of Health and Human Services: National Institute of Arthritis and Musculoskeletal and Skin Diseases [NIAMS], 2004).

RA is estimated to affect approximately 2.1 million people in the United States, about 1% of the adult population, and similarly about 1% of the population worldwide. RA affects a variety of races and ethnic groups (Harris, 2005; Silman, 2001; U.S. Department of Health and Human Services: NIAMS, 2004). Women are

2-3 times more likely than men to become afflicted with the disease. Onset typically occurs between the ages of 35 and 50 years; however, children and young adults can also develop the disease (Cush, Kavanaugh, & Stein, 2005; Silman, 2001).

Symptoms

The degree and severity of symptoms of RA varies between individuals. The classic features of RA include warm and tender joints, as well as symmetrical joint involvement (U.S. Department of Health and Human Services: NIAMS, 2004). This symmetrical pattern of joint involvement means that if the right wrist is affected, then typically the left wrist will be involved, as well. The wrists, fingers and small bones of the hands are the most frequently affected joints; however, ankles, feet, knees, and hips are often involved. RA can involve any diarthrodial joint, also called a synovial joint, which is defined as a freely movable joint (Pugh et al., 2000).

RA has the potential to affect the form and function of many otorhinolaryngologic joints, such as the ossicular joints located in the ear, the temporomandibular joint, and the cricoarytenoid joints (Gairola et al., 1991; Harris, 2005; Kovarsky, 1984; Rigual, 1988). Similar to ossicular joints, the cricoarytenoid joint is a true diarthrodial joint and a high occurrence of rheumatoid laryngitis has been documented (Brazeau-Lamontagne, Charlin, Levesque, & Lussier, 1986; Kolman & Morris, 2002; Papadimitraki, Kyrmizakis, Kritikos, & Boumpas, 2004; Voulgari, Papazisi, Bai, Zagorianakou, Assimakopoulos, & Drosos, 2005). Despite the prevalence of otorhinolaryngologic complications of RA, the main manifestations of the disease often cause ENT symptoms to be overlooked by both patients and physicians (Papadimitraki et al., 2004).

Individuals with RA often experience morning stiffness, pain and stiffness following long periods of rest, in addition to fatigue and fevers (Cush et al., 2005). Individuals with osteoarthritis, a type of arthritis that is caused by the breakdown and eventual loss of the cartilage in the joints, typically do not experience symmetrical joint involvement, general feelings of illness and fever, and warm swollen joints experienced by individuals with RA.

RA is a chronic, progressive disease that varies between and within individuals. Some individuals may have mild and moderate forms of the disease, while others can experience severe disease involvement leading to serious joint damage and disability. Individuals with RA often experience periods of worsening symptoms and increasing disease involvement, which are referred to as “flares” or “flare-ups.” Similarly, individuals with RA may also experience improving symptoms and periods of relief from symptoms, called “remissions” (U.S. Department of Health and Human Services: NIAMS, 2004).

Etiology

The exact cause of RA is unknown; however, research has identified several factors involved with RA. Persons with certain genetic factors may have a predisposition for the development of the disease. There is an increased rate of occurrence in first-degree relatives of patients with RA (Silman, 2001), which is approximately four times that of the general population (Cush et al., 2005).

Environmental factors may also contribute to the development of RA. While the exact triggers are unknown, environmental triggers such as a viral or bacterial infection may cause the disease to develop in individuals who are genetically

susceptible (U.S. Department of Health and Human Services: NIAMS, 2004). The inflammation and joint damage caused by RA is associated with tumor necrosis factor (TNF). TNF is a protein produced by the immune system in response to potential toxins, such as endotoxins that originate internally. Recent treatment options have aimed to block TNF action and have proven to be beneficial at improving inflammation in individuals with RA (Moots & Jones, 2004).

Hormonal and gender factors also contribute to an individual's susceptibility to RA. The higher prevalence of women developing RA suggests an effect of sex hormones (Cush et al., 2005; U.S. Department of Health and Human Services: NIAMS, 2004). Pregnancy has also been found to improve RA symptoms in some females (Silman, 2001), and symptoms may flare following pregnancy (U.S. Department of Health and Human Services: NIAMS, 2004). In addition to hormone levels changing in association with pregnancy, it is believed that the immune system molecules interleukin 12 (IL-12) and tumor necrosis factor-alpha (TNF- α) also change as a result of pregnancy, contributing to development of RA in susceptible individuals (U.S. Department of Health and Human Services: NIAMS, 2004). Anecdotal reports have also suggested an influence of menstrual cycle on the severity of symptoms associated with RA (Silman, 2001).

Diagnoses

There is no single test that diagnoses RA. Instead, a test battery including case history, physical examination, and laboratory tests contribute to the diagnosis of the disease. Due to the similarity of RA symptoms to other diseases such as Reiter's syndrome, Lyme disease, systemic lupus erythematosus (SLE), and polyarticular

gout, differential diagnosis is important for accurate identification of the disease (Cush et al., 2005). A complete and comprehensive medical history, including the patient's description of symptoms, disease onset, and joint function, are important to aid in proper diagnoses. A physical examination assesses the presence of common RA features such as swollen, tender joints and loss of joint function, as well as reflexes and muscle strength (U.S. Department of Health and Human Services: NIAMS, 2004). The joints often affected by RA are the following: proximal interphalangeal (PIP) joints located at the middle of the finger; metacarpalphalangeal (MCP) joints located at the first knuckle of the hand; and metatarsophalangeal (MTP) joints located at any of the joints between the metatarsals and the phalanges in the foot (Pugh et al., 2000).

Laboratory tests for RA include testing for rheumatoid factor (RF). RF is an antibody that is present in 75% to 80% of individuals with RA (Cush et al., 2005), and is detected by a blood test. Not all individuals with RA test positive for RF and not all individuals who have tested positive for RF develop the disease (U.S. Department of Health and Human Services: NIAMS, 2004). RF is also present in individuals with conditions other than RA such as Sjögren syndrome, hepatitis, and SLE (Cush et al., 2005).

Additional laboratory tests are often used to support an RA diagnosis. A blood test is used to check levels of white and red blood cells. Individuals with RA often have a low red blood cell count causing anemia, and a high white blood cell count which signals infection in the body (Moots & Jones, 2004). An erythrocyte sedimentation rate (ESR, or "sed rate") may be performed to measure inflammation

in the body. ESR measures how quickly red blood cells fall to the bottom of a test tube. The faster the sedimentation rate, the more inflammation that is present in the body. High sedimentation rates in individuals with RA reflect greater disease activity. C-reactive protein (CRP) testing is also conducted to measure inflammation in the body by measuring the amount of CRP produced by the liver. High levels of CRP reflect inflammation in the body, and this test is commonly used to monitor inflammatory conditions, such as RA. A specific type of CRP test, high-sensitivity CRP, further evaluates risks for sudden heart problems. Higher levels of CRP reflect a greater severity of RA (Moots & Jones, 2004). ESR and CRP levels measure active inflammation and may be helpful for assisting in diagnosis. These measures are also useful to estimate a prognosis as well as to gauge the effectiveness of therapy (Cush et al., 2005).

X-rays and other imaging techniques are employed to assess the degree of joint destruction. Such images can provide information about the swelling of joints and the destruction of bone surrounding the joints (Hunder, 1999). After only months of disease involvement, a loss of cartilage and bony erosions may develop. Within the first two years of the disease, 70% of patients will develop bony erosions (Cush et al., 2005). Imaging may also be useful to assess the progression of the disease (U.S. Department of Health and Human Services: NIAMS, 2004).

While the test battery approach helps to contribute to diagnosis of the disease, the American Rheumatism Association (ARA) outlined revised criteria in 1987 for the classification of RA (Arnett et al., 1988; Silman, 1988). According to Arnett et al. (1988), the sensitivity and specificity of this criterion was 91.2% and 89.3%,

respectively; however, when the evaluation criterion was applied during the first year of disease onset, the sensitivity and specificity dropped to 80.9% and 88.2% respectively.

RA can also be classified into active or inactive disease staging. The inactive phase uses the same criterion as active RA, based on the American Rheumatism Association (Arnett et al., 1988). The inactivity of the disease is determined when an individual that formerly presented with the classic afflictions is currently asymptomatic (Silman, 2001).

Pharmacological Treatment

There is no cure for RA but there are a variety of treatment methods and approaches. The goals of treatment approaches are to improve individuals' functionality, relieve pain and inflammation, and slow down or stop joint damage (U.S. Department of Health and Human Services: NIAMS, 2004).

Most individuals with RA take medication to control the disease and to reduce pain and inflammation. Common types of drug treatment include the use of the following: disease-modifying antirheumatic drugs (DMARDs) to slow the course of the disease (e.g., methotrexate; hydroxychloroquine); non-steroidal anti-inflammatory drugs (NSAIDs) to reduce inflammation (e.g., ibuprofen, acetaminophen, aspirin); corticosteroids to relieve inflammation and swelling (e.g., prednisone); and biologic response modifiers such as TNF inhibitors (e.g., etanercept, infliximab) and interleukin-1 inhibitor (e.g., anakinra) that block cytokines, a part of the immune system that contributes to inflammation (Moots & Jones, 2004; U.S. Department of Health and Human Services: NIAMS, 2004). Possible ototoxic effects have been

found in patients treated with large dosages of aspirin, but most individuals' hearing recovers following discontinuation of the drug (Halla & Hardin, 1988). In addition, Kastanioudakis et al. (1995) reported no correlation between sensorineural hearing loss and the common antirheumatic medications NSAIDs, D-penicillamine, plaquenil and methotrexate.

Extra-articular manifestations

Extra-articular manifestations tend to occur in patients with severe and longstanding RA who have tested positive for RF (Moots & Jones, 2004). Some extra-articular manifestations may include heart and lung involvement, muscle weakness, nodules, and vasculitis (Harris, 2005; Maini & Feldmann, 1998). Rheumatoid nodules are subcutaneous masses consisting of fibrous tissues that can vary from a soft mobile mass to a hard, rubbery mass. While they are not often painful, nodules are commonly found in areas susceptible to trauma, such as elbows and hands (Maini & Feldmann, 1998), and can range in size from that of a pea to a walnut (Hunder, 1999). Vasculitis is a non-infectious inflammatory disorder involving the blood vessels (Maini & Feldmann, 1998). Vasculitis is usually found in the most severely affected individuals and can involve large and small vessels (Harris, 2005). It has been hypothesized that the middle ear changes in RA may be associated with vasculitis impacting the blood supply to the incus. The most susceptible part of the ossicular chain is believed to be the long process of the incus, which has a tenuous blood supply, and interference with the flow of blood may lead to joint erosion and discontinuity (Camilleri, 1991). Vasculitis may also potentially affect the blood supply to the cochlea and cochlear nerve, causing a sensorineural

type of hearing loss (Öztürk et al., 2004). McCabe (1979) first introduced the topic of autoimmune sensorineural hearing loss, which has been associated with vasculitis; however, this involvement typically produces a rapidly progressive hearing loss that may occur suddenly.

Middle Ear

Middle Ear: Anatomy

The two joints located in the middle ear, the incudomalleolar and incudostapedial, are freely movable diarthrodial joints. Therefore, the middle ear joints may be subject to rheumatic involvement similar to other joints in the body. The incudomalleal joint is formed by the articulation of the head of the malleus and the head of the incus (Lipscomb, 1996). This saddle-shaped diarthrodial joint glides in response to pressure changes in the normal middle ear (Hüttenbrink, 1998). The incudostapedial joint is formed by the articulation of the long process of the incus and the head of the stapes and is a ball and socket joint (Gussen, 1971). Attached to the ossicular chain are the stapedius and tensor tympani middle ear muscles. The contraction of the stapedius and tensor tympani muscles, which can be activated by vocalizations, chewing, yawning, tactile stimulation, and relatively intense sounds (acoustic reflex), stiffens the middle ear system. One hypothesized function of this response is protection of the auditory system by reducing the sound levels that reach the inner ear (Sesterhenn & Breuninger, 1978). A change in this protective function is theorized by some researchers as contributing to the higher prevalence of sensorineural hearing loss in individuals with RA (Öztürk et al., 2004)

The function of the middle ear system is to transform acoustical energy into mechanical energy, and to transmit that mechanical energy to the fluid of the cochlea. The ossicular chain and the ossicular joints are important components in the transmission of sound through the middle ear system, transmitting and boosting the signal received from the tympanic membrane to the cochlea. This energy transfer starts when sound waves enter the ear canal, creating sound pressure, which vibrates the tympanic membrane (Wiley & Stoppenbach, 2002). The medial movement of the tympanic membrane causes the manubrium of the malleus to move medially, and the head of the malleus to move laterally. This in turn causes the body of the incus to move laterally and the lenticular process to move across the head of the stapes, pushing the footplate in and out of the oval window. When the tympanic membrane moves laterally, the reverse and opposite phase occurs (Lipscomb, 1996). The flow of energy through the system depends upon the acoustic impedance/admittance of the system and the acoustic and mechanical contributions from the anatomic structures in the system.

The middle ear plays an important physiological role in the auditory system's ability to overcome the impedance mismatch between the air in the ear canal and the fluid in the cochlea through the area effect, the leverage effect involving the ossicles, and the curvature of the tympanic membrane. Pathology and systemic diseases influence the effectiveness of the middle ear transmission of sounds through the system.

Middle Ear: Diagnostic Tests

Impittance Measurement Principles. Acoustic immittance is a collective term that refers to the ease of flow of energy [admittance (Y_a)] in a system, the opposition to the flow of energy [impedance (Z_a)] in a system, or both (American National Standards Institute, 1987; Shanks, Lilly, Margolis, Wiley, & Wilson, 1988).

Factors that affect the opposition with which energy flows through the system (impedance) include resistance (R) and reactance (X). Resistance is the opposition to the flow of energy created by friction in the system and causes some of the energy in the system to be dissipated as heat. Reactance is the opposition to the flow of energy by parts of the system that store energy and involves the compliance and mass of the system (Shanks et al., 1988).

Resistance properties are affected by air movement and friction created by the tendons and ligament of the middle ear (Shanks & Shelton, 1991). Reactance properties are influenced by two components: mass reactance and compliant reactance. Compliant reactance is related to the structures that store energy due to their stiffness. Mass reactance is related to structures that store energy due to their inertia or mass. Factors that influence the compliance or stiffness of the middle ear system include the tympanic membrane, round window membrane, ossicular ligaments, and middle ear muscles, in addition to the air within the ear canal and middle ear cavity. The mass contributions of the middle ear system include the ossicles, pars flaccida of the tympanic membrane, and the perilymph in the cochlea (Shanks & Shelton, 1991; Van Camp, Margolis, Wilson, Creten, & Shanks, 1986). Unlike resistance, reactance is frequency dependent. The effects of stiffness are

greater for lower frequencies while the effects of mass are greater for higher frequencies. The overall impedance of the middle ear system is dependent on a combination of the resistance, mass reactance and stiffness reactance components (Shanks, 1984).

Admittance, the reciprocal of impedance, has correlates to the impedance components that affect the transmission of energy through the middle ear system. Conductance (G) is the reciprocal of resistance and susceptance (B) is the reciprocal of reactance (Shanks et al., 1988). Conductance is independent of frequency, whereas, susceptance measurements are frequency dependent. Mass exerts the greatest influence at high frequencies and stiffness exerts the greatest influence at low frequencies (Wiley & Stoppenbach, 2002). These components influence the ease of energy flow through the ear. Current immittance instruments measure the admittance of the middle ear system. Clinically, an acoustic immittance test battery includes tympanometric and acoustic reflex measurements, to assess the functioning of the middle ear system.

Single-frequency tympanometry. Tympanometry is an objective measure that records the changes in acoustic immittance in the external ear canal in response to air pressure changes in the ear canal (Shanks et al., 1988). Since the commercial development of an acoustic-impedance bridge in 1963 (Zwislocki, 1963) and the publication of the first clinical paper by Jerger (1970), single frequency tympanometry has routinely been used clinically to assess middle ear function. Tympanometry most commonly measures the admittance of a signal through the middle ear system, although impedance and other measurements can be made as well.

The most simple and common form of tympanometry utilizes a single probe tone of 220- or 226-Hz (Lilly, 2005). Low frequency tympanograms have been interpreted by the classification of tympanometric shape (Jerger, 1970; Jerger & Jerger, 1974; Liden, 1969; Vanhuysse, Creten & Van Camp, 1975), or by quantitative measurements comparing tympanometric width, equivalent ear canal volume and static admittance to available normative values (Shanks et al., 1988). The most popular classification method was proposed by Jerger (1970), which categorizes tympanograms based on shape. Type A tympanograms have peak pressures near atmospheric pressure, and are further classified according to peak height: A_s are described as shallow tympanograms due to reduced peak height; A_d are described as deep tympanograms due to increased peak height; and A are described as normal due to normal peak height. The type B tympanogram does not have a measurable peak and is flat or round in shape, and the type C tympanogram has a normal peak height but negative peak pressure. Figure 1 displays an example of a Type A (normal) tympanogram, which was obtained from a participant in this study. This classification scheme provides a gross description of measurements, and remains popular today despite its limitations and the availability of quantitative measures (Fowler & Shanks, 2002).

Tympanograms are often analyzed based on comparison of quantitative values, as opposed to only shape classification. These quantitative measures include peak compensated static admittance (height of the tympanogram at which the peak occurred), tympanometric peak pressure (TPP) (pressure value at which the peak

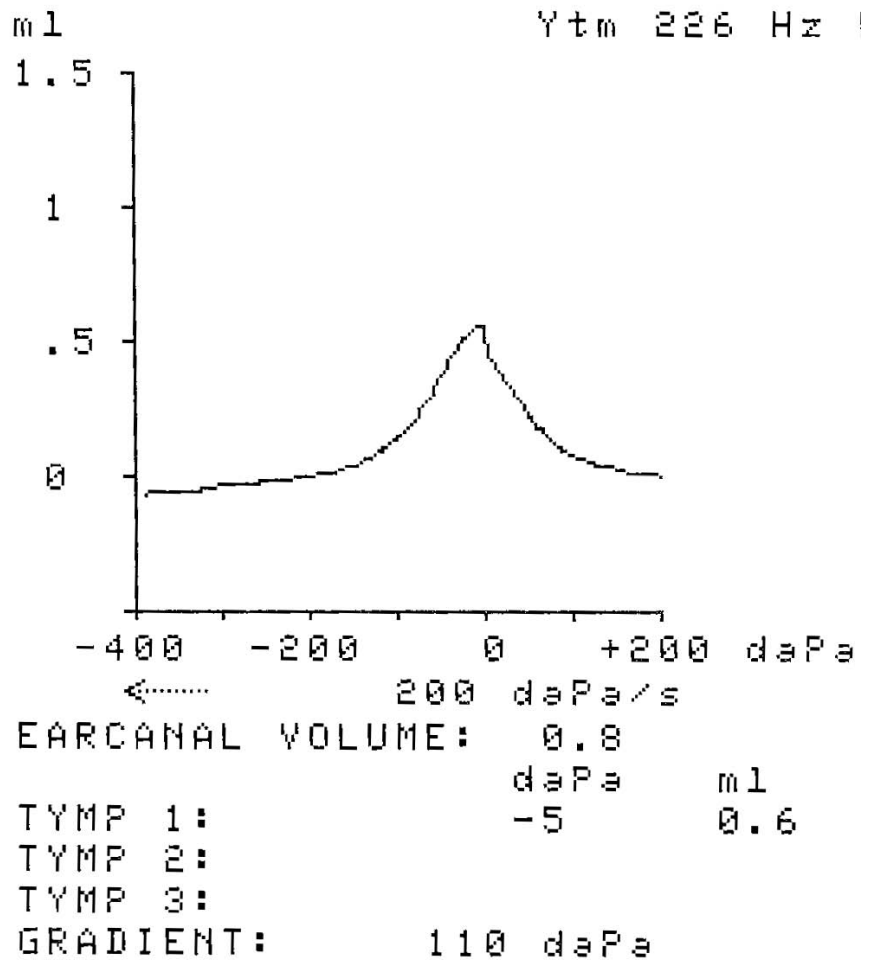


Figure 1. Type A (normal) tympanogram recorded using a 226 Hz probe tone from a 59 year-old male participant in the RA group from the current study. Single-frequency (226 Hz) tympanograms are typically plotted with admittance (shown here in ml) as a function of pressure in the ear canal (in daPa).

occurred), and tympanometric width (pressure interval of the tympanogram at the 50% reduction in peak admittance). Figure 2 highlights the quantitative measures of a normal tympanogram obtained from a participant in the current study.

A normal range of peak compensated static admittance in adults is 0.3 – 1.7 ml (Margolis & Goycoolea, 1993). Tympanometric width is considered normal in adults if it is within a range of 51 – 114 daPa (Margolis & Heller, 1987). Tympanometric width is not widely used clinically in adult populations, and has been more regularly used in detecting middle ear effusion in children (Nozza, Bluestone, Kardatze, & Bachman, 1992). The TPP is the pressure at which the greatest amount of energy is admitted into the middle ear. This is assumed to occur when the pressure in the ear canal is equivalent to that in the middle ear; and, therefore, TPP is used as an estimate of middle ear pressure. This measure is often used to assess Eustachian tube functioning. Poor Eustachian tube functioning often results in negative pressure in the middle ear and, therefore, a negative TPP.

Tympanometry conducted with a single, low-frequency probe tone has proven validity in assessing Eustachian tube function and in identifying tympanic membrane abnormalities (e.g., excessive scarring, perforations) and certain middle ear pathologies (e.g., middle ear effusion) (Onusko, 2004; Shahnaz & Polka, 1997). These measurements have been particularly helpful in the evaluation of young children who are prone to otitis media (Jerger, 1970; Onusko, 2004), but using a single frequency probe tone has several limitations.

Results obtained using 226-Hz tympanometry are dominated by the movement of the tympanic membrane and, therefore, do not always accurately assess

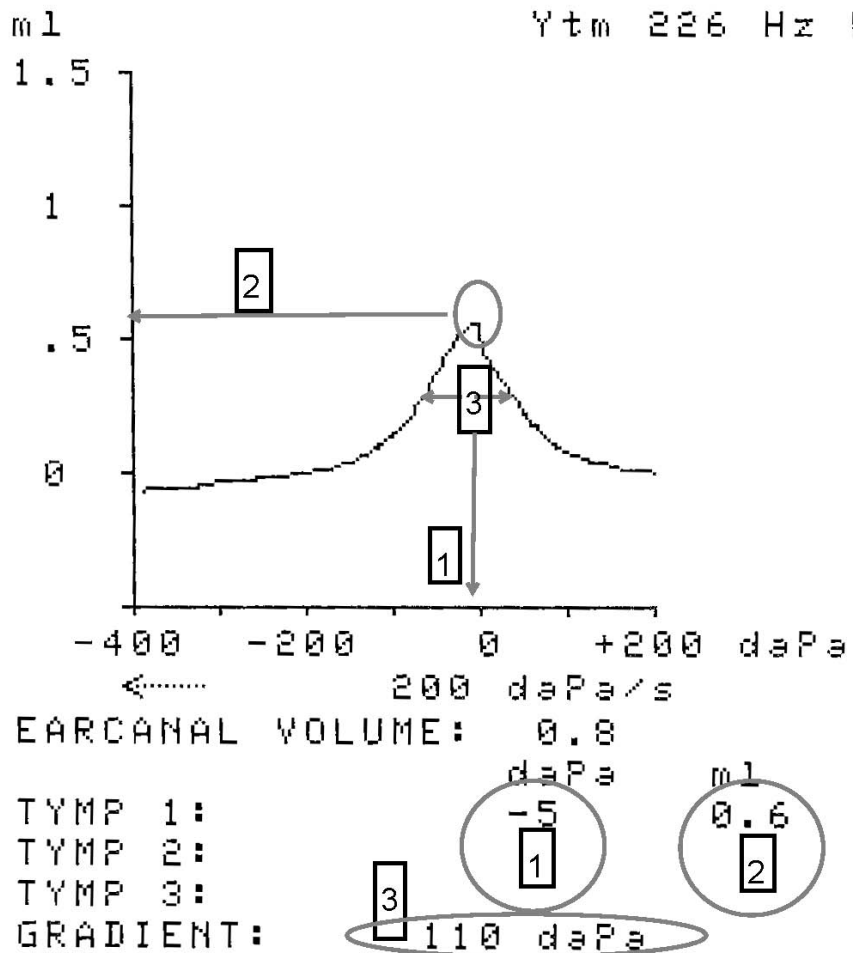


Figure 2. Quantitative measures for a normal 226-Hz tympanogram recorded from a 59 year-old male participant in the RA group from the current study. Measure 1 identifies the tympanometric peak pressure (TPP) of -5 daPa. Measure 2 identifies the peak compensated static admittance of 0.6 ml. Measure 3 identifies the tympanometric width of 110 daPa.

the function of the ossicular chain (Shahnaz & Polka, 1997). Additionally, a standard, single, low-frequency tympanogram does not accurately distinguish ears with normal middle ear function and ears with otosclerosis, a pathology that causes a stiffening of the middle ear (Colletti, 1976; Hunter & Margolis, 1992).

The inadequacies of single frequency tympanometry are due in part to limited information provided about the middle ear, which is a frequency dependent system (Colletti, 1976; Hunter & Margolis, 1992). Low frequency tympanometry assesses a normally functioning middle ear when it is a stiffness-dominated system, meaning that the middle ear has greater compliance reactance than mass reactance. Similar to how a threshold measured at 500 Hz provides insufficient information about the hearing sensitivity of the auditory system, a single probe tone provides insufficient information about sound transmission through the middle ear system.

Multiple frequency tympanometry. Additional tympanometric measures can be obtained using higher probe tone frequencies up to 2000 Hz. Commonly used additional frequencies are at 660/678- and 1000-Hz. Tympanograms obtained using higher probe tone frequencies are often analyzed according to shape because they can have a variety of configurations, unlike the typical single peak found in normal adults for low-frequency probe tones. Low-frequency probe tone tympanograms most often measure admittance. As previously discussed, there are several factors that contribute to the admittance measured: stiffness and mass (susceptance) and friction (conductance) of a system. Susceptance (B) and conductance (G) tympanograms are often measured separately at higher frequency probe tones due to the greater influence of the mass of the system.

Liden (1969) first described the multi-peaked or notched configurations of multi-frequency tympanometry. Vanhuysse et al. (1975) created a classification model to explain the shapes obtained from tympanograms recorded at 678-Hz. Margolis, Van Camp, Wilson, and Creten (1985) extended the model to compare tympanograms recorded at different probe frequencies. The authors found tympanometric shapes followed an orderly progression as frequency increased, and produced more complex patterns at higher probe frequencies. The notching (“W” shape) of the tympanogram indicates the middle ear system becoming progressively more mass dominated (Shanks et al., 1988). The susceptance (B) tympanogram is expected to notch first as frequency is increased, followed by the conductance (G) tympanogram. There are four classic Vanhuysse et al. (1985) patterns based on the number of maxima and minima peaks: 1B1G, 3B1G, 3B3G, and 5B3G. Examples of some of these tympanogram types are shown in Figures 3, 4 and 5.

When the middle ear system is stiffness controlled, the susceptance component is positive. When the middle ear system is mass controlled, the susceptance component is negative. This model suggests that if the susceptance tympanogram is either un-notched or notches and the center of the notch is above the tail value, then the middle ear is stiffness-dominated. In contrast, if the tympanogram notched and the center notch is below the tail value, then the middle ear is mass-dominated. When the susceptance notch is equal to the tail value, then the mass and compliance are equal and the middle ear is in resonance.

The resonant frequency is the frequency at which mass and compliance susceptance are equal. The resonant frequency can be found in a variety of ways;

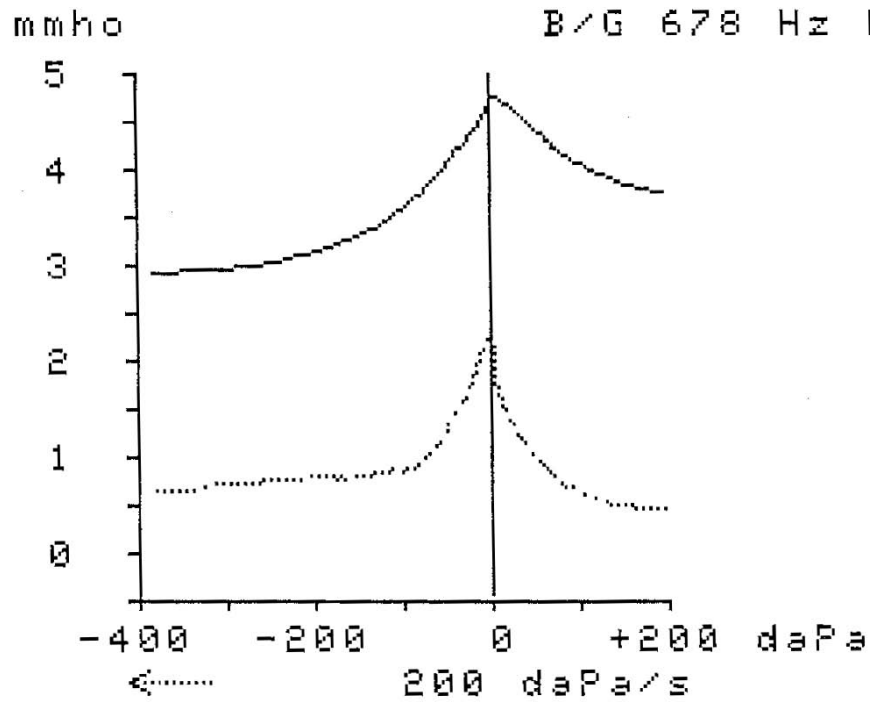


Figure 3. Example of a 1B1G type pattern from data obtained by the current study, and classified based on Vanhuyse et al. (1975). Single peaked tympanograms without the presence of notching were observed at 678-Hz in this 58 year-old female participant from the NC group. The susceptance curve (B) is on top and the conductance (G) curve is on bottom.

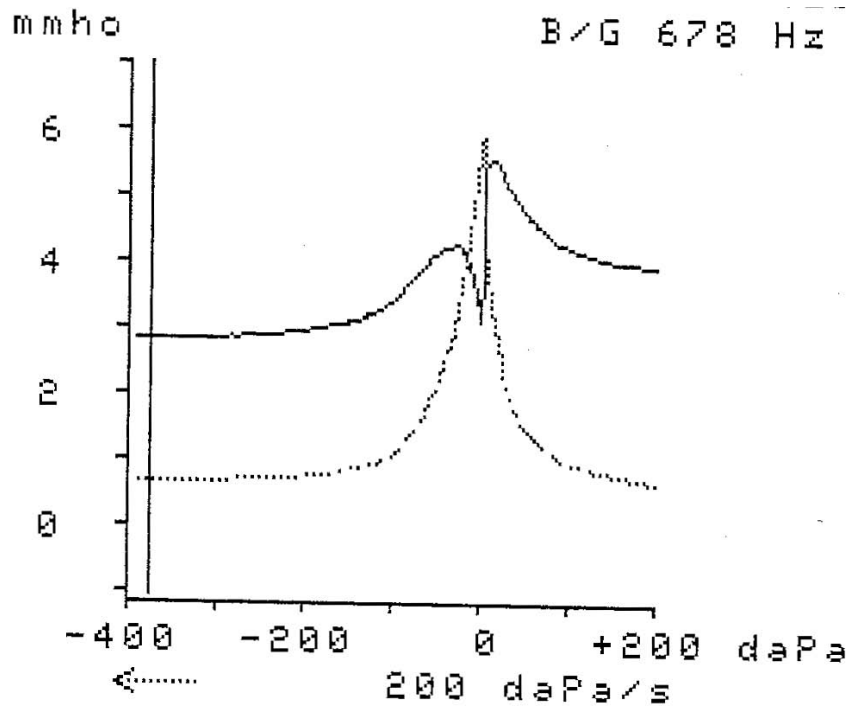


Figure 4. Example of a 3B1G type pattern from data obtained by the current study, and classified based on Vanhuyse et al. (1975). Notching was observed in the susceptance curve at 678-Hz in this 58 year-old female participant from the NC group, while the conductance curve remained single-peaked. The susceptance curve (B) is on top and the conductance (G) curve is on bottom.

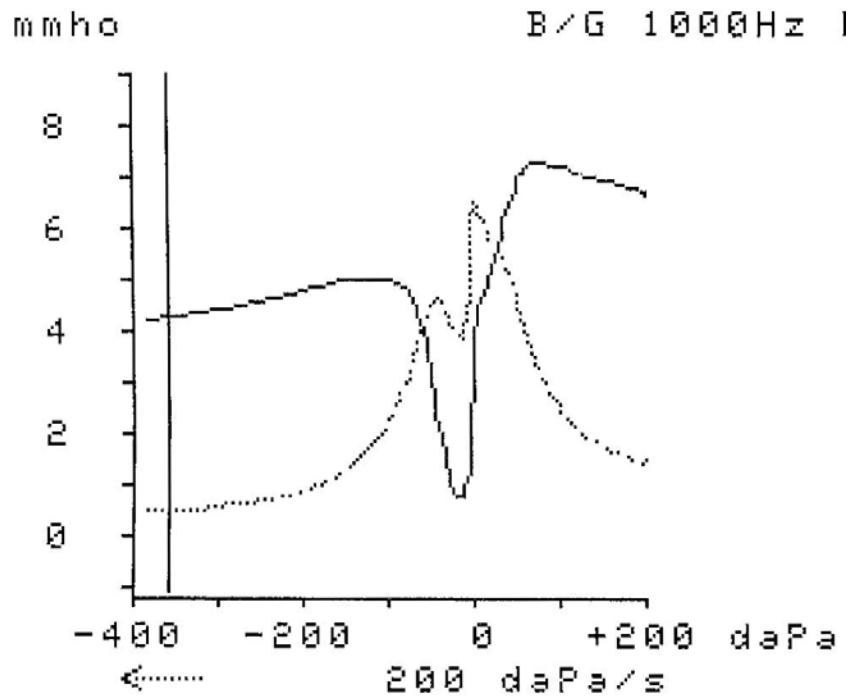


Figure 5. Example of a 3B3G type pattern from data obtained by the current study, and classified based on Vanhuyse et al. (1975). Notching was observed in both the susceptance and conductance curves at 1000-Hz in this 59 year-old female participant from the RA group. The susceptance curve (B) starts at +200 daPa on top and the conductance (G) curve starts at +200 daPa on bottom.

however, standard clinical immittance equipment typically assesses resonant frequency by using either a sequential frequency sweep or a sequential pressure sweep to determine the point at which compensated susceptance is equal to zero (Shanks et al., 1988). The method used to determine the resonant frequency, frequency sweep or pressure sweep, can influence the values obtained (Shanks, Wilson, & Cambron, 1993).

According to Colletti (1976), the average normal adult middle ear resonance is approximately 1000-Hz; however, studies have found a large range of normal values. Using a sweep frequency method, the 90% range for compensated resonant frequencies has varied. Margolis and Goycoolea (1993) reported a range of 800-2000 Hz in 28 adults aged 19-48. Hanks and Mortensen (1997) reported a range of 650-1300 Hz in 53 young adults aged 18-25. Holte (1996) reported a range of 630-1250 Hz in 144 adults aged 20-90. Shahnaz and Davies (2006) reported a range of 500-1120 in 76 young adults aged 18-34. In theory, a pathology that increases the stiffness of the middle ear system, such as otosclerosis, should cause the middle ear impedance to remain dominated by stiffness over a broader frequency range than normal, and thus causes the resonant frequency of the middle ear to be higher than normal. Conversely, a pathology that increases the laxity of the middle ear system, such as ossicular discontinuity, should cause the middle ear impedance to become mass controlled and the resonant frequency will be lower than normal (Shanks et al., 1988).

The use of multifrequency tympanometry and determination of resonant frequency is clinically useful in the identification of middle ear pathologies (Colletti,

1976; Hunter & Margolis, 1992; Shahnaz & Polka, 1997). Resonant frequency is more sensitive than 226-Hz tympanometry for identification of ears with otosclerosis and ossicular discontinuity (Hunter & Margolis, 1992; Shahnaz & Polka, 1997; Valvik, Johnsen, & Laukli, 1994). Additionally, peak static admittance values of higher-frequency tympanograms may also be compared to normative values (Calandruccio, Fitzgerald, & Prieve, 2006; Shahnaz & Davies, 2006) to provide further clinical utility. However, there is limited normative data available.

Additionally, there are limitations in the diagnostic abilities of multifrequency tympanometry. One issue is the wide range of normal middle ear resonant frequencies (Valvik et al., 1994). Valvik et al. (1994) compared resonant frequencies from individuals with tympanosclerosis, otosclerosis, and stapedectomy to a group of normal individuals. While statistically significant differences were measured between groups, large overlap occurred across groups with the normal ears ranging from 350-1750 Hz. However, the inclusion criteria for the normal controls were not clearly defined. The test-retest reliability was within 150 Hz for most individuals, although larger test-retest differences were found in several participants. The authors believed these differences were attributable to a flat susceptance slope close to the point at which susceptance is equal to zero, resulting in small variations causing a change in resonant frequency.

When examining the fine structure of the middle ear resonance, Hocke et al. (2000) found there may be more than one resonant frequency, possibly helping to explain the broad range of normal results and the difficulties with using middle ear resonance as a diagnostic measure. Another limitation with this measurement method

is the limited frequency range of 200 – 2000 Hz. Frequencies above 2000 Hz cannot be evaluated using tympanometry due to difficulties encountered from distortion of acoustic sources, precise impedance calibration, and standing waves (Allen, 1986). Therefore, multi-frequency tympanometry cannot be tested at these higher frequencies due to artifact (Holte & Margolis, 2002).

Wideband Reflectance

Wideband reflectance is a more recent approach for measuring middle-ear function. It allows assessment of middle ear function over a broader frequency range, including frequencies above 2000 Hz. Wideband reflectance was first introduced by Allen (1985) who described a system capable of measuring the impedance magnitude using Thevenin parameters for the acoustic source transducer, allowing the impedance to be calculated from the pressure measured in the delivery tube. Allen was able to measure impedance magnitude up to 33,000 Hz in cats.

The reflectance of the middle ear system is estimated by comparing the impedance at the probe tip (using Thevenin values) and the characteristic impedance of the ear canal (Feeney, 2005). Wideband reflectance measurements can examine a variety of sound transmission properties including energy transmittance, power absorption, and ER. When measuring ER, there are two basic sound waves in the ear canal: (a) the sound from the probe traveling toward the tympanic membrane; and (b) the sound reflected by the tympanic membrane traveling outward. The reflection coefficient, r , is the ratio of these two waves, (b/a) (Feeney, 2005). ER is calculated as its magnitude squared, $|R|^2$, and represents the ratio of reflected to incident energy (Mimosa Acoustics, 2005; Voss & Allen, 1994). The energy absorbed, also known as

energy transmittance, is equal to one minus the energy reflectance (Feeney, 2005). To date, ER is the most commonly analyzed measurement of wideband reflectance and the majority of the research has examined results using ER.

ER values can range from 0.0 to 1.0 (Keefe, Ling, & Bulen, 1992) and may also be presented as a percentage based on the operating system used (Mimosa Acoustics, 2005). An ear with high impedance would reflect energy from the middle ear, and the reflectance would be very high (close to 1.0 or 100%). A middle ear that easily absorbs energy would reflect little to no energy, and the reflectance would be very low (close to 0.0 or 0%). Figure 6 shows an example of a typical ER measurement obtained in a participant from the NC group in this study. Figure 7 shows an abnormal ER measurement from an excluded participant that presented with negative tympanometric peak pressure of -280 daPa, which was well outside the inclusion criteria of ± 10 daPa tympanometric peak pressure required in this study.

The “abnormal” ear displayed in Figure 7 has low reflectance values throughout the low-frequencies, suggesting more sound is absorbed than in a “normal” ear. The reflectance pattern also produced an atypical configuration with multiple peaks at high frequencies. This demonstrates that the sound reflected by the middle ear varies considerably in the high frequencies. The differences between these two figures reflect the importance of accounting for middle ear pressure. ER measurements are typically obtained at ambient pressure.

Based upon Allen’s measurement system (1985), several researchers have since measured ER in humans and determined ER was accurate at frequencies over 10,000 Hz (Keefe et al., 1992; Keefe, Bulen, Arehart & Burns, 1993; Voss & Allen,

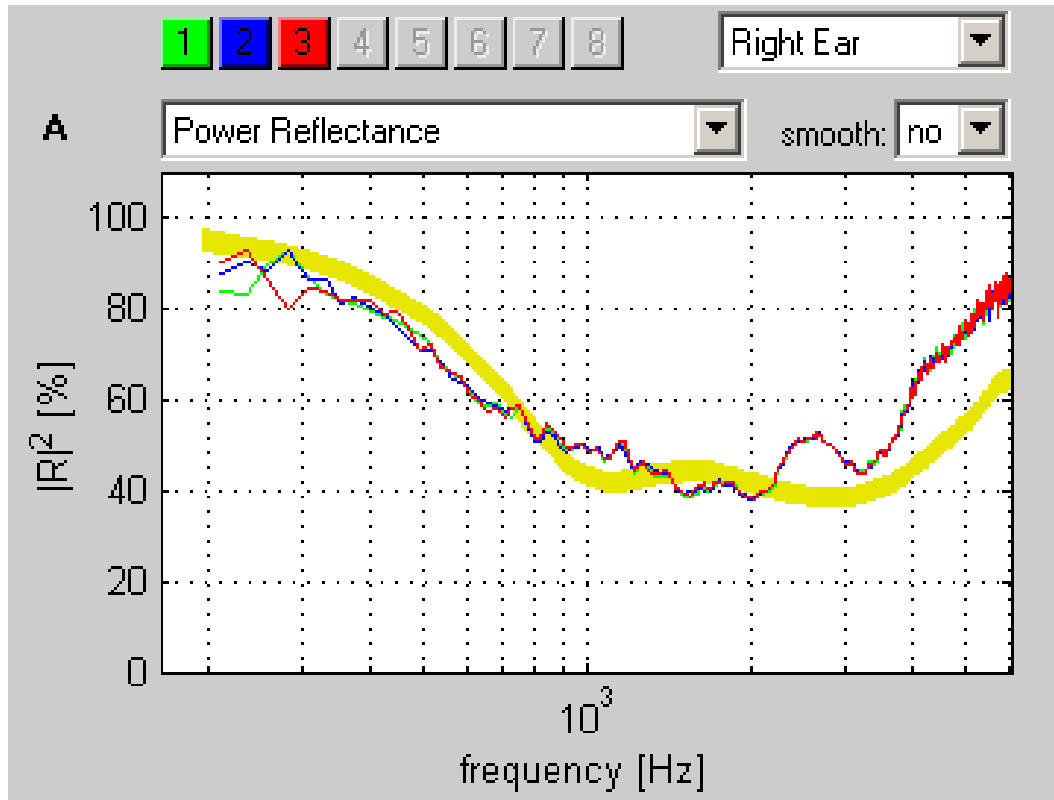


Figure 6. ER measurement recorded from a 42 year-old female from the NC group in this study. This figure represents a “normal” ER response. The three, thin, overlapping lines represent the three ER test runs. The average of three runs is used to calculate the ER for data analyses. The thick line represents normative data from Voss and Allen (1994).

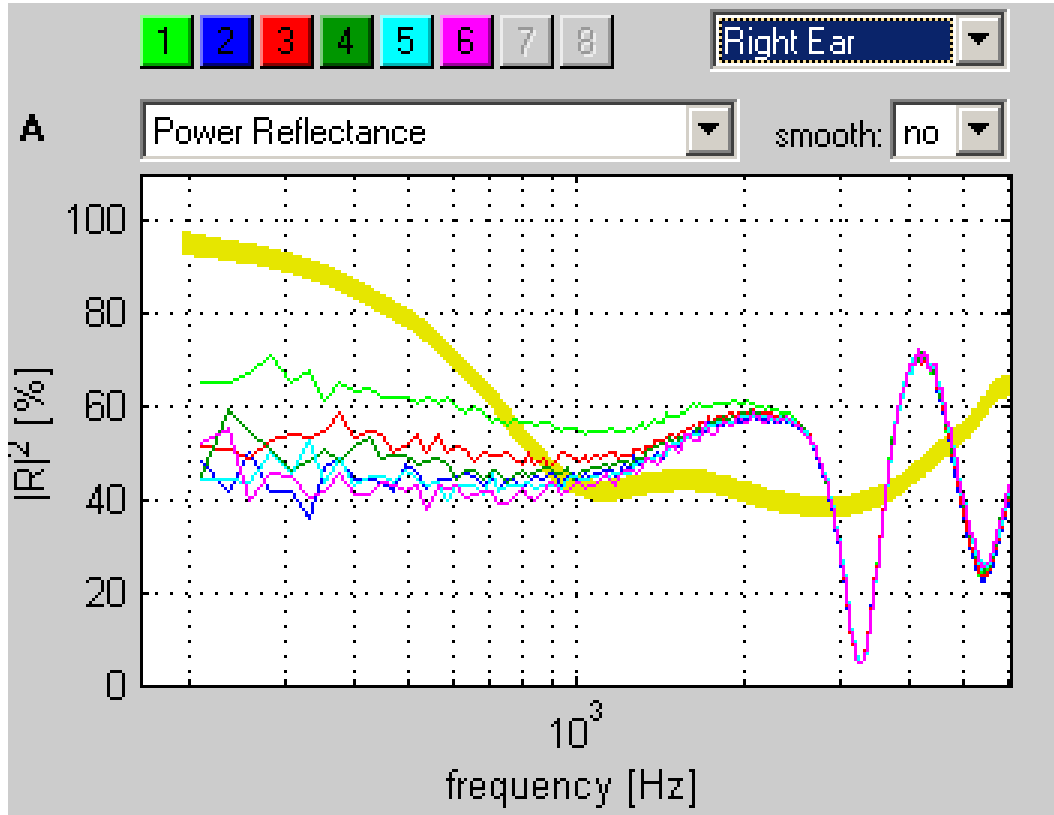


Figure 7. ER measurement recorded from a 41 year-old female who was excluded from this study due to negative tympanometric peak pressure (-280 daPa), as recorded by a 226-Hz tympanogram. This figure represents an “abnormal” ER response. The thin, overlapping lines represent each ER run. The thick line represents normative data from Voss and Allen (1994).

1994). Keefe et al. (1992) used the Thevenin approach to measure data on closed, cylindrical tubes. Results indicated this approach was a well-suited approach for measurement in human ear canals. This led to studies measuring ER in adult populations, as well as populations such as infants in which standard immittance measures have proven difficult to use.

Normative Values in Adults

Keefe et al. (1993) and Voss and Allen (1994) measured ER in humans and established a basis of adult normative values for future studies. Keefe et al. (1993) measured impedance and reflection coefficients in 10 adults and reported that the least amount of energy was reflected around 3000-4000 Hz and the most around 7000 Hz. This showed that a normal ear absorbed the most sound around 3000-4000 Hz. Voss and Allen (1994) reported similar ER values in their study of 10 normal hearing young adults, but reported a large amount of intersubject variability. However, neither study reported measurements of middle ear pressure, which can affect ER measurements obtained at ambient pressure.

Similar findings were reported for normal adults by Margolis, Saly, and Keefe (1999), Feeney, Grant and Marrayott (2003), Feeney and Sanford (2004) and Shahnaz and Bork (2006). These researchers measured the averaged ER values across 20, 75, and 40 ears, respectively. The group mean results indicated high ER in the low frequencies, lowest ER values around 4000 Hz, and increasing ER values at higher frequencies. Preliminary studies have examined the test-retest reliability of ER measurements and good test-retest reliability was reported (Hunter, 2004; Vander Werff & Prieve, 2004). The patterns of ER results between these studies conducted at

ambient pressure were similar, although some differences were found. This may be due to differences in equipment. Shahnaz and Bork (2006) were the only investigators to use a commercially available reflectance system, Mimosa Acoustics. All other studies used a system developed by Keefe et al. (1992). Differences may also be attributed to participant selection. Feeney et al. (2003) and Feeney and Sanford (2004) reported using only individuals with TPP ± 10 daPa. In Margolis et al. (1999) and Shahnaz and Bork (2006), the researchers did not report the TPP values for their participants. Participants with TPPs that deviate significantly from ambient pressure may have impacted the results. The variance across studies may also be due to varying sample sizes, and the different age distribution of participants.

When comparing normative data, it is also important to consider potential effects of aging. Currently, only Feeney and Sanford (2003, 2004) have studied potential effects of advanced age on middle ear function using ER. The authors compared 40 young adults (aged 18 – 28) and 30 older adults (aged 60-85), and examined 226-Hz tympanometry and ER. While they found no effects of aging using 226-Hz tympanometry, they observed significant differences between older and younger adults on ER and impedance values measured by the ER system. The study found a decrease in ER from 800 to 2000 Hz, and an increase around 4000 Hz. The older adult group exhibited less ER at frequencies below the point of least ER, and more ER above the point of least ER, suggesting a decrease in the stiffness of the middle ear system with age.

Energy Reflectance (ER) and Middle Ear Disorders

ER has many potential benefits for evaluating middle ear disorders. Much of the work in this area has been focused on ER measures in patients with otitis media (OM). The effectiveness of ER as a clinical tool to identify a conductive hearing loss was studied by Piskorski, Keefe, Simmons and Gorga, (1999). In this study, the test group was comprised of 92 children aged 2-10 years who were seen at the Boys Town National Research Hospital ENT clinic. Children with symptoms of otitis media were compared to asymptomatic children. However, the presence or absence of a conductive component was not confirmed with an otologic exam, but rather based solely on the presence of an air-bone gap determined by masked bone-conduction thresholds, which can be difficult to assess in young children. The effectiveness of ER measurements obtained at ambient pressure was compared to a 226-Hz tympanogram. Comparing the tests separately, the ER responses alone better predicted the presence of a conductive hearing loss than tympanometry alone. In addition, the authors found that ER scores at 2000 and 4000 Hz more accurately predicted a conductive impairment than at 500 Hz, supporting the hypothesis that the 2000-4000 Hz frequency range is a sensitive indicator of middle ear function.

The ability of ER to predict conductive hearing loss was expanded to include older children and adult populations by Keefe and Simmons (2003). The authors examined acoustic transfer function measurements obtained at ambient-pressure and pressurized conditions, and compared them to 226-Hz tympanometry to assess the predictive accuracy of each measurement. Using acoustic transfer functions such as pressure, ER, acoustic admittance, and acoustic impedance, Keefe and Simmons

(2003) compared 42-normal ears (ages 10-48, M = 19.2 years) and 18-hearing-impaired ears (ages 11-55, M = 30.3 years). The ages of the two groups were not comparable, and the group with normal ears was younger overall. The hearing-impaired ear group included those with sensorineural, mixed and conductive hearing losses. The nature of the conductive hearing losses was not known for this study; therefore, results were examined only for the ability to detect a conductive hearing loss and not to diagnose the type of conductive hearing loss. Both acoustic transfer function measurements, ambient pressure and pressurized conditions, were more sensitive predictors of conductive hearing loss than standard tympanometry. While the pressurized measurements may have even more accuracy when identifying disorders that involve negative middle ear pressure, ambient pressure measurements were sufficiently accurate to use as a hearing-screening application.

The detection of otitis media with effusion (OME) in children with ER measurements has many advantages over conventional clinical measurements. Hunter (2004) reported significantly higher ER in children from birth to 2 years of age with middle ear effusion, compared to children without effusion and with normal middle ear function. The authors suggested this measure might improve test performance over standard tympanometry. Jeng, Levitt, Lee and Gravel (2001) used ER measurements to compare the ears of three children with OME to 15 children with normal ears aged 2.5-5 years of age. They found that generally ears with OME showed less power absorption, and close to zero absorption below 1000-Hz, indicating the increased stiffness caused by the pathology in the low frequencies. Results obtained between 1000-6000 Hz showed significantly less resistance than

those observed in the control group. However, due to the small sample size of impaired ears in this preliminary study, it is difficult to draw strong conclusions. These preliminary data suggest that wideband reflectance provides more frequency-specific information regarding the peripheral auditory system as well as a better understanding about the transmission of sound across a broader range of frequencies important for speech. ER measurements in patients with OM have reflected increased ER, consistent with this pathology, which reduces the flow of energy through the middle ear.

Several studies have examined the effectiveness of ER as an identification tool in the presence of OM or OME; however, few studies have examined other middle ear disorders. Feeney et al. (2003) studied the ability of ER to detect a variety of middle-ear disorders. This study assessed middle ear ER at ambient-pressure in 10 adults: two individuals with sensorineural hearing loss (one with normal middle ear pressure and the other with negative middle ear pressure), and conductive losses caused by a variety of conditions, including otitis media with effusion, otosclerosis, disarticulation of the ossicular chain, hypermobility of the tympanic membrane, and perforation of the tympanic membrane. These individuals were compared to 40 young adults with normal hearing. The ER measurements for the individual with otitis media indicated that nearly all energy was reflected back at frequencies from 250-3000 Hz, similar to the findings of Jeng et al. (2001). In the two cases of otosclerosis, ER results were abnormal, exhibiting a higher-than-normal ER at frequencies below 1000-Hz. ER was more sensitive to the presence of otosclerosis than the 226-Hz tympanogram, which only identified one case as abnormal.

However, the limited number of participants makes it difficult to draw strong conclusions. ER measurements for the case of ossicular discontinuity exhibited a low-frequency notch at 678-Hz. In addition, the ears of individuals with tympanic membrane perforations absorbed a great deal of energy in the low frequencies, but in the higher frequencies results were near normal. The individual with negative middle ear pressure (-105 and -155 daPa) produced high ER in the low frequencies, reflecting most of the sound energy. This pattern was similar to the individuals with otosclerosis, demonstrating the importance of a correction for middle ear pressure. The results from this study suggest that ER is a promising tool for diagnosis of middle-ear disorders, but that more information is necessary.

Data from Allen, Jeng, and Levitt (2005) also suggest that ER may aid in identification of middle ear disorders. While this study mainly served as a review of the development of the Mimosa Acoustics System, a commercially available ER measurement tool, it also compared an individual with otosclerosis and an individual with a perforated tympanic membrane to a normal control. In the otosclerotic ear, the stiffening of the ossicles caused a large amount of the energy to be reflected back, as compared to normative values around 2000 Hz. Between 400 and 2000 Hz the normalized resistance in the otosclerotic ear was significantly below that of normal middle ear resistance, and comparable to the results obtained by Feeney et al. (2003). The individual with an eardrum perforation exhibited an erratic power ER pattern that varied widely across frequencies compared to normative values, particularly in the higher frequency range. However, this varied from the results of two ears with tympanic membrane perforations reported by Feeney et al. (2003). While both graphs

display erratic patterns, the low frequency ER range differed between studies. Allen et al. (2005) reported high ER at 200 to approximately 750 Hz, and was more similar to normative data than to Feeney's results. Feeney et al. (2003) reported almost no ER in the same low-frequency range, but his results were different between the two ears tested. The results between studies were more comparable above 1000 Hz.

The use of ER measurements has also been extended to examine the relationship between higher frequency middle ear function and hearing sensitivity. ER measurements were used to compare individuals with varying thresholds at ultra-high frequencies (8000-20,000 Hz) with and without a history of chronic otitis media. Margolis, Saly and Hunter (2000) compared three groups of children: group one included 12 ears from eight children without a history of otitis media; group two included 29 ears of 24 children with a history of otitis media and better ultra-high frequency hearing compared to the group three; and group three included 29 ears of 25 children with a history of otitis media and poorer ultra-high frequency hearing compared to group two. The authors found no differences in middle ear impedance and ER between groups. The use of ER was helpful in supporting the hypotheses that the extended high frequency hearing loss related to otitis media is cochlear in origin.

Additional studies are needed to assess larger groups with a variety of middle ear disorders. The research examining a range of middle ear disorders is limited to a few studies, which did not make statistical comparisons due to small sample sizes (Allen et al., 2005; Feeney et al., 2003). These studies made comparisons of the general shape of the ER frequency curves between individuals with middle ear disorders to normative data. Additionally, some of the research findings are still

considered preliminary in nature (Hunter, 2004; Jeng et al., 2001; Vander Werff & Prieve, 2004).

Despite the limited amount of research, the studies that have been conducted indicate the promise of ER as a more sensitive measure than standard tympanometry to detect changes in the middle ear system and the presence of middle ear disorders. ER has demonstrated benefits for testing difficult populations such as infants, due to the system's capability to test a higher frequency range. The ability of ER to identify middle ear disorders that are often missed by standard middle ear measures, such as otosclerosis, demonstrates the potential benefits of the system to elucidate and clarify middle ear abnormalities that may be present, but not typically detected by other middle ear measurements.

Rheumatoid Arthritis (RA) and the Auditory System

RA and Hearing Loss

Rheumatic involvement of the auditory system and the potential effects on hearing sensitivity has been widely debated. Researchers have discussed three potential causes of hearing loss in individuals with RA: (a) rheumatic involvement of middle ear joints; (b) sensorineural damage subsequent to neuritis or vasculitis; and (c) ototoxicity of drug treatments (Elwany et al., 1986; Frade & Martin, 1998; Kastanioudakis et al., 1995; Magaro et al., 1990; Öztürk et al., 2004). Neuritis is an inflammation of the nerve and vasculitis is an inflammation of a blood or lymph vessel (Pugh et al., 2000). Neuritis and vasculitis are potential extra-articular manifestations of RA and may affect the cochlea or the cochlear nerve (Magaro et al., 1990). Researchers have also hypothesized the involvement of vasculitis in the

middle ear, resulting in the decreased mobility of one or both ossicular joints as a result of the disease process affecting the blood supply to the lenticular process of the incus (Biasi, Fiorino, Carletto, Caramaschi, Zeminian, & Bambara, 1996; Camilleri, 1991; Colletti, Fiorino, Bruni, & Biasi, 1997; Goodwill, Lord & Knill-Jones, 1972).

Copeman (1963) was the first to publish an article identifying the link between RA and hearing loss. Copeman studied three patients with RA who had fluctuating hearing loss associated with increased disease severity. Two of these participants had documented conductive hearing loss with a negative history of middle ear disease. Copeman hypothesized that the conductive hearing loss was caused by an inflammation in the synovial fluid lining the joint articulations in the middle ear, interfering with sound transmission. This claim was strengthened when hearing sensitivity improved with a decrease in rheumatic symptoms. Following Copeman's research, many studies have examined the influence of RA on hearing sensitivity.

General findings across the literature have indicated that individuals with RA exhibit a variety of hearing loss types (Özcan et al., 2002; Raut et al., 2001; Salvinelli et al., 2004; Salvinelli, D'Ascanio, Casale, Vadacca, Rigon, & Afeltra, 2006). This is not surprising considering the varied potential causes of hearing loss in individuals with RA. Several studies have reported a higher prevalence of sensorineural hearing loss compared to normal controls (Goodwill, Lord, and Knill-Jones, 1971 & 1972; Kastanioudakis et al, 1995; Magaro et al., 1990). A higher prevalence of abnormal middle ear findings that do not result in a conductive hearing loss but that often

coincide with the presence of sensorineural hearing loss have also been reported (Elwany et al., 1986; Reiter et al., 1980; Takatsu et al., 2005).

Initial studies investigating RA and hearing loss reported a high prevalence of hearing loss; however, variables such as salicylate usage and otologic history were often poorly controlled. Heyworth and Liyanage (1972) tested 33 individuals with RA, aged 26-83 years old, and found a higher prevalence of hearing loss compared to the general population. For most participants, the reported onset of hearing loss occurred after the development of RA. A variety of hearing loss types were reported. The authors accounted for age-related decreases in hearing by classifying subnormal hearing based on age-appropriate normative data from Hinchcliffe (1958).

Audiological results revealed over 36% of the participants presented with hearing loss: three participants had a mixed or conductive hearing loss and nine had a sensorineural hearing loss. These researchers did not control for salicylate usage, which was believed to have contributed to the cases of sensorineural hearing loss. They also did not control for individuals with a significant otologic history, and, therefore, may have missed other potential causes of the conductive and mixed hearing losses. Despite these noted limitations, the authors suspected an association between RA and hearing loss.

Djupesland et al. (1973) tested 48 patients with a variety of rheumatic joint diseases (RA, juvenile RA, ankylosing spondylitis, psoriatic arthritis), and compared results to a normal control group of 50 participants with the same sex and age distribution. The majority (35/48) of the patients were diagnosed with RA. Overall, eight individuals with a rheumatic joint disease had a conductive hearing loss and five

had a sensorineural hearing loss. The presence of the conductive hearing loss coincided with an abnormal middle ear system as assessed by impedance measures. However, the specifics used to define hearing loss and normal middle ear measures, as well as the use of statistics were poorly described. The authors attributed the conductive hearing loss to inflammatory rheumatoid joint diseases and questioned whether the sensorineural losses were due to ototoxic effects from salicylates.

Results of more recent studies in which the researchers controlled for participants' otologic history and the use of ototoxic medications have continued to find all types of hearing loss in the RA populations. General findings across studies have reported a higher percentage of hearing loss compared to age and gender matched controls (Özcan et al., 2002; Raut et al., 2001; Salvinelli et al., 2004; Salvinelli et al., 2006). However, no differences between specific audiometric measurements in RA and age and gender matched controls have also been reported (Halligan, Bauch, Brey, Achenbach, Bamlet, McDonald, & Matteson, 2006). The hearing loss is typically bilateral, although unilateral hearing loss has also been observed, and both unilateral and bilateral hearing losses are typically mild to moderate in degree (Özcan et al., 2002; Raut et al., 2001).

Several studies have reported all types of hearing loss among their samples of patients with RA. Özcan et al. (2002) and Raut et al. (2001) examined the hearing sensitivity in individuals with RA (35-38 participants) and found sensorineural hearing loss in 26-60%, conductive hearing loss in 17-26%, and mixed hearing loss in 10-47% of the study participants. A higher prevalence of conductive involvement was reported by Özcan et al. (2002) compared to Raut et al. (2001), which may be a

result of the different criteria used to classify the presence of a conductive component [air-bone gap greater than 5 dB (Özcan et al., 2002) versus air-bone gap greater than 20 dB (Raut et al., 2001)].

Similarly, Salvinelli et al. (2004) reported that in the RA group, 10/38 had sensorineural hearing loss, 21/38 mixed hearing loss and 7/38 had a conductive hearing loss. These results indicated that every individual in the RA group had hearing loss. The authors stated that most individuals had an air-bone gap, but did not state what they considered to be a significant air-bone gap. They reported most of the participants with RA (28/38) had conductive involvement, but the limited details regarding criteria to define hearing loss make comparisons with other studies difficult. A more recent study by this group of authors also reported a higher prevalence of hearing loss in the RA group compared to an age- and gender-comparable NC group (Salvinelli et al., 2006). Criteria for a significant air-bone gap were not defined, and a wide variety of hearing loss types were reported. Twenty-four of the 28 participants with RA had hearing loss, and of these hearing losses 10 were sensorineural, eight were mixed, and six were conductive. Salvinelli et al. (2006) reported exclusion criteria based on a significant otologic history; however, due to the presence of air-bone gaps, four of the individuals with RA underwent stapedectomy surgery. The researchers reported a closure of the mean air-bone gap, which changed from 11 dB HL pre-operatively to 2 dB HL post-operatively in these individuals. Across studies, air- and bone-conduction thresholds were poorer in the RA populations compared to the control groups (Özcan et al., 2002; Salvinelli et al., 2004; Salvinelli et al., 2006), with significant differences in low- to mid-frequency air

conduction thresholds (500-2000 Hz) (Raut et al., 2001; Salvinelli et al., 2004), and in bone conduction thresholds at all test frequencies (250-4000 Hz) (Özcan et al., 2002; Salvinelli et al., 2004).

In comparison to those studies that found a variety of hearing loss types, some studies have found a higher incidence of only sensorineural hearing loss in RA populations (Goodwill et al., 1971 & 1972; Kastanioudakis et al, 1995; Magaro et al., 1990). Based on pure-tone audiometric results, several researchers reported that 44-55% of the individuals with RA tested had sensorineural hearing loss (Kastanioudakis et al, 1995; Magaro et al., 1990). The pure-tone results indicated that these individuals had bilateral hearing loss of mild degree. However, Magaro et al. (1990) included only participants with normal Type A tympanograms, which may account for the lack of conductive-type hearing impairments. In addition, the high prevalence of hearing loss reported by Kastanioudakis et al. (1995) may be attributed to presbycusis and not to RA. The authors defined hearing loss as hearing thresholds greater than 20 dB HL at two or more frequencies without accounting for potential effects of aging, despite the fact that 14 of their 45 participants were over 60 years old.

Still other studies have also indicated a high prevalence of both sensorineural hearing loss and abnormal middle ear function in individuals with RA (Elwany et al., 1986; Reiter et al., 1980; Takatsu et al., 2005). The results reported by Elwany et al. (1986) and Takatsu et al. (2005) indicated that approximately one-third of the individuals with RA tested had sensorineural hearing loss, and that many of the participants with RA had reduced middle ear admittance indicating an increased

stiffness of the middle ear system (Elwany et al., 1986; Kakani et al., 1990; Takatsu et al., 2005). However, the individuals with abnormal tympanograms did not necessarily have sensorineural hearing loss. The hearing loss in individuals with RA was generally a mild bilateral loss. Significant threshold differences were noted between individuals with RA and controls in the lower and mid frequencies, 250-2000 Hz, and at 4000 Hz (Takatsu et al., 2005). This finding is similar to the results of Raut et al. (2001) and Öztürk et al. (2004), who also reported significant changes in the higher-frequency regions. Takatsu et al. (2005) found a significant difference in air-bone gaps at 250 and 500 Hz between groups without reporting any conductive hearing loss, but the criteria for a conductive component used in the study was an air-bone gap greater than 20 dB at two or more frequencies. Therefore, these stringent criteria may account for the lack of reported conductive involvement. The audiometric results reported by Reiter et al. (1980) were consistent with the higher prevalence of hearing loss reported by many other studies; in addition, almost 60% of individuals with RA had abnormal tympanograms with either an increase or decrease in stiffness. The researchers also reported three instances of conductive hearing loss in the group of individuals with RA, which typically coincided with an increased laxity of the middle ear system. Individuals with sensorineural hearing loss also had tympanograms that indicated an increase in the laxity of the middle ear system. The high rate of middle ear abnormalities was believed to contribute to the increased rate of hearing loss in individuals with RA. The high prevalence of hearing loss may result from systemic inflammation and tissue injury as a result of RA involvement,

but this involvement typically is not significant enough to result in a measurable conductive component (Takatsu et al., 2005).

One study has also indicated an effect of RA on ultra-high frequency hearing sensitivity. Öztürk et al. (2004) reported a higher rate of sensorineural hearing loss for individuals with RA at ultra high-frequency regions. Ultra-high frequency thresholds were assessed up to 16,000 Hz in 74 participants with RA. The researchers from this study reported higher thresholds in participants with RA across all frequencies compared to a group of 45 normal controls of the same age and gender distribution. Most notably, ultra high-frequency sensorineural hearing loss was found in individuals with RA and the severity of ultra high-frequency hearing loss correlated with longer disease duration.

Another study indicated differences in transient evoked otoacoustic emissions (TEOAEs) recorded in individuals with RA compared to an age and gender comparable NC group (Salvinelli et al., 2006). Salvinelli et al. (2006) reported decreased reproducibility and amplitude of TEOAEs in the RA group compared to the NC group. However, 14/28 of the individuals in the RA group had a conductive component that would affect the measurement of TEOAEs, making it difficult to determine whether the differences were due to middle ear abnormalities or outer hair cell function in the inner ear.

Evidence in the literature points toward a trend for greater auditory involvement among those individuals with more advanced disease involvement. Fluctuating sensorineural hearing loss associated with disease severity and “flare-ups” of disease inflammation have been reported in case studies (Liening and

Larouere, 1997; Nores & Bonfils, 1988). In the study conducted by Özcan et al. (2002), the participants were grouped according to disease stage using the Steinbrocker functional classification index (Steinbrocker, Traeger, & Batterman, 1949). A higher incidence of hearing loss was found among participants with RA that had greater disease severity. A higher prevalence of sensorineural hearing loss in individuals with RA was found in those who had nodules compared to those without nodules (Goodwill et al., 1971 & 1972; Takatsu et al., 2005). Magaro et al. (1990) found that the presence of sensorineural hearing loss significantly correlated with active RA compared to an inactive disease stage. They also found a significant correlation between individuals who had tested positive for rheumatoid factor and poorer hearing thresholds. Salvinelli et al. (2006) reported a significant inverse correlation between disease duration and TEOAE amplitude. Takatsu et al. (2005) classified the RA groups according to disease severity and staging, and found a significant difference in ESR rates between individuals with RA and hearing loss, compared to individuals with RA and no hearing loss. This finding suggested that individuals with high levels of inflammation might be more likely to have auditory involvement. However, this issue is also debated among researchers, similar to many other aspects involving auditory function and RA. Other studies have reported finding no influence of RA disease activity or duration on hearing loss (Goodwill et al., 1971 & 1972; Kakani et al., 1990). It should be noted that in the report by Takatsu et al. (2005) the value of inflammation levels as determined by ESR in individuals with RA was very low and participants did not present with common

extra-articular manifestations such as nodules, indicating that many of the individuals did not have severe disease manifestations.

Ototoxicity has been cited as another potential cause of hearing loss in patients with RA. While there are numerous pharmacological treatment options for RA, the research addressing ototoxicity has been quite limited. Researchers have acknowledged the common use of potentially ototoxic medications such as salicylates and loop diuretics for treatment of RA (Goodwill et al., 1971 & 1972; Heyworth & Liyanage, 1972; Mukerji, Esterm & O'Sullivan, 1994). As would be expected, when individuals with RA discontinued the use of salicylates, hearing sensitivity returned to normal limits, indicating only temporary ototoxic effects (Heyworth & Liyanage, 1972). No significant differences were found between individuals with RA who had previously taken salicylates and those who had not (Goodwill et al., 1971), suggesting only current use of salicylates might potentially affect hearing sensitivity.

More recent pharmacological treatment of RA often involves nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) (Moreland, 2004; U.S. Department of Health and Human Services: NIAMS, 2004). While studies have cited the possible influence of ototoxicity on hearing loss in individuals with RA, it has been difficult to separate and identify the various potential causes of hearing loss. Little evidence exists regarding the effects of potentially ototoxic medications used to treat this population. A single study, Kastanioudakis et al. (1995), found no correlation between sensorineural hearing loss and the common antirheumatic medications NSAIDs, D-penicillamine, plaquenil and methotrexate. However, while few studies examined potential damage caused by

long-term use, RA medications have also been used to treat and restore sudden hearing loss in individuals without RA or inflammations. The use of several RA medications such as prednisone (Haberkamp & Tanyeri, 1999) and more recently TNF inhibitors and methotrexate may help restore and improve hearing in individuals with autoimmune inner-ear disease that experienced a sudden hearing loss (Street, Jobanputra, & Proops, 2006).

RA and Middle Ear Function

Researchers have reported a high prevalence of abnormal middle ear function in individuals with RA, but the effects on middle ear function have varied (Elwany et al., 1986; Öztürk et al., 2004; Takatsu et al., 2005). Abnormalities reported in the literature on this topic have included an increased stiffness of the middle ear system (Biasi et al., 1996; Colletti et al., 1997; Elwany et al., 1986; Öztürk et al., 2004; Takatsu et al., 2005) as well as increased laxity of the middle ear system (Moffat et al., 1977; Rosenberg et al., 1978). The presence of abnormal middle ear systems has not consistently correlated with effects on hearing thresholds in individuals with RA. Generally, individuals with conductive hearing loss have an increase in the laxity of the middle ear system, although a clinically significant conductive hearing loss is rare in this group (Raut et al., 2001). The majority of studies suggest the most common effect is increased stiffening of the middle ear system that may not necessarily coincide with hearing loss (Elwany et al., 1986; Öztürk et al., 2004).

Several reports of visual inspection of the middle ear space through surgical intervention and temporal bone autopsy have provided compelling evidence of potential RA involvement in the middle ear joints (Goodwill et al., 1972; Gussen,

1977). In a case study of a man with RA undergoing surgery for a unilateral conductive hearing loss, Goodwill et al. (1972) noted that the ossicular chain was intact and there were no visible signs that would cause a conductive hearing loss. Due to the normal appearance of the middle ear system, the authors theorized the probable cause of the conductive hearing loss was rheumatic involvement. Atypical lesions of the incudomalleal and incudostapedial joints were found in a woman with long-standing RA and sicca syndrome (Sjögren Syndrome) (Gussen, 1977). In a case study of this 55-year old woman, a temporal bone autopsy revealed striking changes in the ossicular joints. The incudomalleal and incudostapedial joints exhibited dissolution of disk material and proliferation of synovial-type elements in the articulations, forming pannus tissue. Unfortunately, audiometric data were only obtained when the woman was 37 and 42 years of age. At the time of audiometric evaluation, a slight bilateral high-frequency hearing loss was present and no further mention of hearing loss was noted in the records.

Standard tympanometric measurements have been used to identify abnormal middle ear systems in individuals with RA, frequently using low-frequency tympanometry analyzed according to the Jerger tympanometric classification system (Jerger, 1970). Several studies suggested an increased stiffness of the middle ear system in individuals with RA, resulting in tympanograms classified as Type A_s (Elwany et al., 1986; Öztürk et al., 2004; Takatsu et al., 2005). Specifically, the researchers reported that about 28% of individuals with RA (Takatsu et al., 2005) and 52-58% of the ears in individuals with RA were classified as having Type A_s tympanograms (Elwany et al., 1986; Öztürk et al., 2004). Although, Takatsu

provided the static admittance values used to define what classified a Type A_s tympanogram (≤ 0.3 ml), Öztürk et al. (2004) and Elwany et al. (1986) did not use quantitative criteria to determine tympanogram classification. When quantitative values were reported by Öztürk et al. (2004), the ranges listed for the RA group closely approximated normal static admittance ranges. They reported more than half of the ears in the RA group had type A_s tympanograms, and that 10.8% and 13.5% of left and right ears, respectively, had type A_d tympanograms, but the static admittance ranged from 0.28-1.6 mL in this group of participants. This range is similar to the range of normal admittance (0.3-1.7 mL) as determined by Margolis and Goycoolea (1993). The values used to determine the criteria for tympanogram typing were not specified in some studies, which make it difficult to compare the results based on the researcher's tympanogram type classification. Despite these limitations, however, Öztürk et al. (2004) reported the RA group had significantly lower admittance values than a group of age and gender comparable NC participants. Elwany et al. (1986) reported that over 70% of the 68 patients with RA had static admittance levels that were reduced to one-half or one-third of normal admittance values; however, the listed compliance ranges were essentially within normal limits (0.29-0.72 cc). Although a high prevalence of sensorineural hearing loss was present in the RA participants, no correlation was found between reduced middle ear admittance and sensorineural hearing loss (Elwany et al., 1986).

Two studies that used multifrequency tympanometry to examine middle ear function in individuals with RA have also reported an abnormally stiff middle ear system. The results obtained using multifrequency tympanometry indicated that 36-

40% of the 30 participants with RA had abnormal middle ear resonant frequencies compared to the control group. Higher resonant frequencies indicated an increased stiffness was the most common type of abnormality, although some cases of an increased laxity were also recorded as indicated by lower resonant frequency (Biasi et al., 1996; Colletti et al., 1997). Both studies only included individuals with inactive disease staging, which may account for the lack of observed hearing loss. Frade and Martin (1998) assessed middle ear function using multifrequency tympanometry, but did not find significant differences between individuals with RA compared to normative data. However, a difference was observed when comparing individuals with active versus inactive disease activity. Individuals with active RA had stiffer middle ear systems indicated by a higher resonant frequency than those individuals with inactive RA, and due to these differences, the authors suggested multi-frequency testing might help to diagnostically determine disease activity.

The trend of increased middle ear stiffness was also observed in children with chronic juvenile RA (Giannini, Marciano, Strano, Alessio, Marcelli, & Auletta, 1997; Siamopoulou-Mavridou, Asimakopoulos, Mavridis, Skevas, & Moutsopoulos; 1990). More than half (10/18) of the children (aged 6-16 years) with juvenile RA in the study conducted by Siamopoulou-Mavridou et al. (1990) had abnormally stiff Type A_s tympanograms, although no audiometric data were collected to determine a potential correlation with hearing loss. This study performed few measurements, testing only 220-Hz tympanograms and acoustic reflexes in the 18 children with juvenile RA and a control group of 14 gender and age matched children. Comparisons were made between groups and based on tympanogram classification.

The authors interpreted these findings to indicate a stiffening of the middle ear system as a result of inflammation of the ossicular joints, and found this most often occurred in patients with the most severe symptoms. Giannini et al. (1997) reported children with chronic juvenile RA ($M = 9.9$, $SD = 5.2$ years) presented with higher middle ear resonant frequencies compared to a control group of 30 healthy children ($M = 7.7$, $SD = 3.6$ years; Giannini et al., 1997). Of interest, all 35 children with RA exhibited normal audiometric thresholds (less than 25 dB HL), normal 226-Hz tympanograms and normal acoustic reflexes. While the increased stiffness of the middle ear system was not detected by low-frequency tympanometry, it was identified through the use of multi-frequency tympanometry.

Although the majority of studies examining middle ear function in patients with RA have indicated increased stiffness of the middle ear system, several researchers have reported tympanometric data that indicated patients with RA had an increased laxity of the middle ear system (Moffat et al., 1977; Rosenberg et al., 1978). Two studies examined middle ear function by using a 660-Hz tympanometry and found 38-42% of individuals with RA exhibited a marked notch in the tympanogram (Moffat et al., 1977; Rosenberg et al., 1978). This finding suggested an abnormally low resonant frequency and, thus, an increased laxity of the middle ear system and/or mass changes in the participants with RA compared to normal controls. While Moffat et al. (1977) did not assess pure-tone thresholds, the audiometric results from Rosenberg et al. (1978) suggested no significant hearing loss in individuals with RA despite the presence of middle ear abnormalities. Raut et al. (2001) compared the presence of notching in 678-Hz tympanograms between RA and NC groups;

however, no statistically significant differences between groups were observed. These authors also measured middle ear function with a 226-tympanogram analyzed according to Jerger's classification system (Jerger, 1970). The results from Raut et al. (2001) revealed that 25.71% (11 ears from 9 individuals) of tested ears in the RA group had high compliance classified as Type A_d and these researchers reported no cases of an increased stiffness of the middle ear system. Although no individuals in the control group exhibited Type A_d tympanograms, the average admittance for the group of individuals with RA and for the control group were not significantly different. The authors suggested that the conductive hearing loss documented in the participants with RA (6/35) was most likely due to a laxity of the middle ear system. However, the most common type of hearing loss recorded by these authors was a sensorineural hearing loss found in 21 individuals in the RA group.

Other researchers have reported both increased stiffness and laxity of the middle ear system in a group of individuals with RA. Reiter et al. (1980) used 660-Hz susceptance tympanograms and converging susceptance patterns for 220- and 660-Hz probe tones to assess middle ear function. Immittance data revealed that almost 60% of the arthritic ears (27 of 46) exhibited abnormal findings; 22% (10 ears) showed an increased laxity from a 660-Hz notched tympanogram, and 37% (17 ears) showed an increased stiffness from a negative-pressure convergence of susceptance function. The RA group in this study had a high rate of hearing loss, 48% (11 individuals) with sensorineural hearing loss and 13% (three individuals) with conductive hearing loss. Two of the individuals with conductive hearing loss had a low resonant frequency, which the authors hypothesized may be a result of an

increase in the effective mass of the system caused by damage to the ligaments that anchor the ossicles. A high rate of sensorineural hearing loss and abnormal middle ear function was also found.

A variety of abnormal tympanometric results were also found by Özcan et al. (2002). The authors reported almost 40% of the 37 participants with RA tested had abnormal tympanograms, according to Jerger's classification system (Jerger, 1970). These abnormal tympanometric results were dispersed across individuals with normal hearing, as well as sensorineural, conductive, and mixed hearing loss. Tympanograms were abnormal in 38% (14/35) of the individuals in the RA group, affecting 23 ears. The tympanograms recorded included: 13 type A_s, 8 type A_d, and 2 type B. The authors suggested a discontinuity of the ossicles was responsible for the conductive hearing loss. The abnormally stiff middle ear systems did not result in a measured conductive hearing loss, but were recorded in some individuals in the RA group with sensorineural hearing loss, as well as individuals with no measured hearing loss.

Despite the varied results in studies assessing middle ear function in individuals with RA, trends across the literature suggest some involvement of the middle ear system in individuals with RA. The findings of middle ear abnormalities suggest possible inflammation of the synovial ossicular joints located in the middle ear, causing an increase stiffness or laxity of the tympano-ossicular system (Giannini et al., 1997; Raut et al., 2001). The rheumatic involvement of the ossicular joint ligaments and capsules may explain both the stiffness and laxity of the middle ear system, depending on how the inflammation affects the joints. Another potential cause is hypothesized to involve the lenticular process of the incus, which may be

affected by vasculitis (Biasi et al., 1996; Camilleri, 1991; Goodwill et al., 1972; Raut et al., 2001; Reiter et al., 1980). This may result in ankylosis or decreased mobility of one or both ossicular joints. There was a high prevalence of middle ear abnormalities that did not coincide with conductive hearing loss, but rather coincided with sensorineural hearing loss (Reiter et al., 1980; Takatsu et al., 2005). It has been hypothesized these abnormalities may reduce the protective mechanism of the middle ear and subsequently result in cochlear damage (Colletti et al., 1997; Öztürk et al., 2004; Raut et al., 2001). The altered motion of the ossicular diathroses reduces the movements of the ossicles and could lead to gradual hair cell damage over time, and possibly make the inner ear more susceptible to potential oto-traumatic agents (Biasi et al., 1996; Colletti et al., 1997). This theory would help to explain the high prevalence of sensorineural hearing loss and middle ear abnormalities observed in individuals with RA.

Summary and Purpose:

Existing literature indicates an increased prevalence of hearing loss in individuals with RA, including conductive, sensorineural, and mixed hearing losses. The most common type of hearing loss is sensorineural that often coexists with abnormal middle ear function (e.g., Takatsu et al., 2005). There remains much debate and speculation about the involvement of the middle ear system and the cause of hearing loss in this population. In part, limited measurements have been used to assess middle ear function in individuals with RA. Middle ear measurements have typically consisted of standard 226-Hz tympanograms that were analyzed based on Jerger's (1970) classification system (e.g., Elwany et al., 1986). The use of such

limited measurements, which have particular inadequacies for pathologies that affect the ossicular chain, may help to explain the wide variety of results in RA research. A few studies have examined multi-frequency tympanometry, and one set of researchers was able to identify changes in stiffness not detected by low-frequency tympanometry (Giannini et al., 1997). The ability to test a broader range of frequencies, as with multi-frequency tympanometry and ER measurements, shows promise for detecting subtle changes in middle ear function.

Chapter 3: Research Questions and Hypothesis

The goals of this study are to provide a comprehensive examination of auditory function in individuals with RA, specifically focusing on the effects of RA on sound transmission through the middle ear using multi-frequency tympanometry and ER. The majority of the existing research on this topic has focused primarily on RA and the presence of hearing loss, thereby assessing auditory function through the use of pure-tone audiometry and basic tympanometry. This study aims to broaden the scope of auditory assessment and focus on the evaluation of middle ear function.

The specific questions addressed by this study include the following:

1. Is there a difference in the prevalence of hearing loss in individuals with RA compared to age- and gender-matched controls? If hearing loss is present, are there qualitative differences in the type of hearing loss between groups?
2. Are there differences in audiometric thresholds between individuals with RA compared to age- and gender-matched controls?
3. Do audiometric thresholds in both groups fall within the range of expected effects of aging on hearing thresholds?
4. Is there a difference between individuals with RA compared to age- and gender-matched controls on the following immittance-based measures of middle ear function:
 - a. Static admittance and tympanometric peak pressure for 226-Hz tympanograms
 - b. Qualitative shape classifications of 678- and 1000-Hz tympanograms
 - c. Calculated static admittance for 678- and 1000-Hz tympanograms

d. Middle ear resonant frequency

5. Is there a difference between individuals with RA compared to age- and gender-matched controls on measures of ER?
6. Is there a difference in DPOAE amplitude levels between individuals with RA compared to age- and gender-matched controls?
7. Does varying level of disease involvement in individuals in the RA group correlate with audiologic measures?

It was hypothesized that the RA group would have poorer auditory thresholds and a higher prevalence of hearing loss compared to the control group and that the type of hearing loss would primarily be sensorineural. It was expected middle ear measurements would reveal a difference between groups, with a greater number of abnormal findings in the RA group compared to existing normative data. However, the types of middle ear abnormalities were expected to include both an increased stiffness and laxity. It was expected that 226-Hz tympanometry would not reveal differences between groups; however, due to the broader frequency range assessed by ER, it was hypothesized this measure would reveal significant differences. Multi-frequency tympanometry was expected to reveal some differences between groups because it has been demonstrated to be more sensitive to middle ear abnormalities than 226-Hz tympanograms, but it was anticipated ER would provide new information about the differences between groups because of the larger frequency range assessed. It was hypothesized that individuals with higher levels of inflammation and a greater number of involved joints would have more middle ear involvement as manifested on measures of middle ear function and hearing loss. It

was anticipated that multi-frequency tympanometry and ER would help clarify the debate surrounding hearing loss and middle ear involvement in individuals with RA by contributing more information about sound transmission through the middle ear in these individuals. These findings could provide insight into the manifestations of this disease in the auditory system as well as the need for inclusion of audiometric evaluations in the standard test battery of individuals with RA.

Chapter 4: Methods

Participants

This is a cross-sectional study examining the audiological differences between two groups: an experimental group of individuals with RA and a control group of age- and gender-matched healthy adults without RA. Twenty-one participants (38 ears) from each group were included in the study. Participants were excluded based on the following criteria: significant history of outer or middle ear pathology (e.g., chronic ear infections) or surgery (e.g., repair of ear drum perforations), head trauma or brain injury, noise exposure, and use of ototoxic medications (e.g., salicylates). Participants were also required to have normal otoscopic examination indicating an ear canal free from excessive cerumen or debris and without visible signs of excessive scarring on the eardrum. Excessive tympanic membrane scarring was defined as the presence of white patches or scar tissue, consistent with tympanosclerosis, as determined by otoscopic inspection performed by the examiner. The same individual performed all otoscopic determinations.

Initially, 25 participants with RA and 23 participants serving as NCs were tested. Four individuals with RA and two individuals from the NC group were excluded based on a significant otologic history (pressure equalization tubes; Eustachian tube dysfunction; tympanic membrane perforation), significant history of noise exposure, head/brain injury (stroke), and/or diagnosis of another type of disease (Psoriatic arthritis) and not rheumatoid arthritis. In addition, three participants had one ear excluded based on otoscopic examination revealing scarring on the tympanic membrane or occluding cerumen. Participants who did not qualify for the study were

given the option to complete the hearing evaluation. Participants were fully informed of all procedures before testing. A sample Consent Form is shown in Appendix A. All participants completed a General Health Questionnaire, which is shown in Appendix B. All individuals in the NC group reported a negative history for any signs or symptoms consistent with RA, as identified by patient responses to the General Health Questionnaire.

The RA group, consisting of 21 participants, ranged in age from 24-64 years old with an average age of 51.10 years, and a standard deviation of 11.52 years. The control group was matched 1:1 based on age (± 1 year) and gender with RA participants. The normal control (NC) group, consisting of 21 participants, ranged in age from 25-63 years old with an average age of 51.14 years, and a standard deviation of 11.30 years. Age did not differ significantly between groups ($t = 0.01$; $p = 0.99$).

The experimental group included adults with RA diagnosed by a physician according to the 1987 American College of Rheumatology classification criteria (Arnett et al., 1988). The RA group was recruited from a natural history study on RA conducted by Dr. Raphaela Goldbach-Mansky at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) at the National Institutes of Health (NIH) in Bethesda, Maryland. The NC group reported a negative history for RA or symptoms similar to RA. The NC group was recruited by flyers and word of mouth.

Otologic history for both groups was obtained through a questionnaire and self-reporting. The medical history for the NC group was obtained through questionnaires and self-report by participants. The medical charts of RA participants were reviewed for current medications, disease duration, joint involvement, and blood

test results for inflammation levels documented by ESR and CRP levels.

Demographic and disease information for RA participants is listed in Table 1.

No participants were currently taking salicylates for treatment of RA. Based on blood test results, ESR rates greater than or equal to 25 mm/hr and CRP and high-sensitivity CRP levels greater than 0.80 mg were considered abnormally high and indicative of high inflammation levels. The blood test results from the RA group were obtained within one week of audiological testing for 18 of the participants, of which 12 were obtained on the same day, and two within three weeks. One patient with longstanding RA (22 years) failed to have blood work completed on the date of audiological testing, but the patient was seen for her physician's exam. In this instance, the patient was classified with inactive disease staging by her physician, and blood work from approximately three months prior to audiological testing and approximately three months following audiological testing were compared. These results were consistent with stable disease activity. The ESR level was 12 mm/hr pre-audiological assessment, compared to 13 mm/hr in a subsequent assessment following audiological evaluation, and CRP was 0.71 compared to 0.74 mg/dL, respectively. All values are consistent with normal levels and inactive disease staging. In this instance, the blood test results from 3 months prior were used because they were obtained closest to the date of assessment. Active versus inactive staging classification was not consistently identified by physicians for all participants; and, therefore could not be further discussed.

The average disease duration of individuals with RA was 13.67 years ($SD = 9.40$) and the average number of swollen joints was 6.62 ($SD = 7.14$). Seventeen of

Table 1

Demographic and Disease Information for RA Participants

	Age-Sex	ESR (mm/hr)	CRP (mg/dL)	High Sens.CRPs (mg/dL)	Rheumatoid Factor	Blood Work (Days)	Number Swollen Joints	Disease Duration (years)	Current Medications			
									NSAID	DMARD	Cortico-Steroids	TNF Inhibitor
	24-F	18	0.79	0.78	+	0	0	6	X	X		
	29-F	13		0.12	-	0	3	7		X		
*	35-F	10		0.08	+	21	7	10		X	X	
**	42-F	27(+)	2.08(+)		-	1	22	8	X	X	X	X
	44-F	28(+)	1.30(+)		+	0	10	18		X	X	X
	45-M	9	<.40		+	0	11	4	X	X	X	X
	47-F	22	<.40	0.11	-	6	2	4		X		
	47-F	12		0.72	+	11	13	10	X	X	X	
	47-F	9		1.30(+)	+	0	0	21		X	X	
	51-F	29(+)		0.30	+	6	18	7		X	X	X
*	57-F	12		1.03(+)	-	0	0	21		X	X	X
	59-F	12	0.40		+	0	4	4		X	X	
**	59-F	40(+)	0.78		+	0	9	8	X	X	X	X
	59-F	12		0.71	+	81	3	22		X	X	X
	59-F	40(+)		0.46	+	0	14	9		X	X	X
	59-M	53(+)	<.40	0.24	+	0	3	30	X	X		X
	60-M	5		0.53	+	4	8	24		X	X	X
	61-F	23		0.23	+	6	0	37		X	X	
	62-F	11		0.23	+	0	0	4		X		
*	63-F	37(+)		0.78	+	7	2	15		X	X	
**	64-M	62(+)		0.33	+	0	0	18		X	X	
Range	24-64	5-62	<0.4-2.08	0.53-1.30		0-81	0-22	4-37				
Mean	51.10	23.10	0.82	0.50		6.81	6.62	13.67				
SD	11.52	15.63	0.60	0.36		17.78	7.14	9.40				

Note. Demographic and disease information for Table 1 was obtained from review of medical charts and blood work results. Positive results for signs of inflammation were designated with a (+). Erythro sedimentation rates (ESRs) were considered positive for values greater than or equal to 25 mm/hr; C-reactive protein (CRP) and high-sensitivity CRP (high sens. CRP) were considered positive for values greater than 0.80 mg/dL. The blood work column represents the number of days between the date of blood work and the date of audiological assessment. The number of swollen joints was obtained from physicians' examination notes. Individuals diagnosed with Sjögren's syndrome are designated by one asterisk (*), and individuals diagnosed with diabetes are designated by two asterisks (**) located next to the first column. The use of current medications such as non-steroidal anti-inflammatory drugs (NSAID), disease modifying antirheumatic drugs (DMARD), corticosteroids, and tumor necrosis factor (TNF) inhibitors were obtained from medical records.

the 21 participants (81%) had tested positive for rheumatoid factor in their medical history. Three individuals were also diagnosed with Sjögren's syndrome, which is an autoimmune disease that destroys moisture-producing glands, and is often associated with rheumatoid arthritis. Three other individuals presented with type II diabetes, although none were taking insulin, and none of these individuals' test results revealed hearing loss.

Not all of the 21 participants in each group could be included in the analyses of acoustic reflexes, ER and DPOAEs. Acoustic reflex thresholds (ARTs) were measurable in 35/38 ears from the RA group, and 37/38 ears from the NC group. ARTs could not be obtained in three ears in the RA group and one ear in the normal control group due to fluctuating static admittance. In addition, another normal control ear had absent reflexes at two frequencies in one contralateral test condition that were unexplained by the presence of a conductive component or degree of hearing loss. Only ears with measurable ARTs were included in this analysis, and the matched participants of the same age and gender from the opposite group were excluded. As a result, 33 ears from 19 participants in each group were included in the analysis of ARTs.

Only that subset of individuals who had tympanometric peak pressure between -10 and $+10$ daPa of ambient pressure as determined by 226-Hz tympanometry were included in ER and DPOAE data analysis. The test equipment, manufactured by Mimoso, tests at ambient pressure, requiring the exclusion of those participants whose tympanometric peak pressure fell outside the -10 to $+10$ daPa range. Sixteen participants (28 ears) from each group were included in this subset,

and were matched 1:1 based on age and gender. Table 2 displays the number of participants and ears that were included in analysis for each measurement.

Procedures

Testing took place in two locations: the Audiology Department in the Clinical Center at the National Institute on Deafness and Other Communication Disorders (NIDCD), National Institutes of Health (NIH) in Bethesda, Maryland and at the Hearing and Speech Clinic and research laboratories, Lefrak Hall, at the University of Maryland College Park. All testing was completed during a single session approximately 1 to 1.5 hours in duration, with the participants seated in a sound booth.

The data collection consisted of audiometric measures, standard immittance measures, multi-frequency tympanometry, ER, and DPOAE measures. The test order was consistent for all participants. Both ears were tested on all participants, and the ear tested first was randomized. Case history and questionnaires were completed first, followed by otoscopy, 226-Hz tympanometry, acoustic reflex thresholds and adaptation, 678-Hz and 1000-Hz tympanograms, and middle ear resonant frequency. After immittance measurements, SRT and air- and bone conduction thresholds were obtained, followed by word recognition. ER and DPOAE measurements were obtained last.

The audiometric measures, standard immittance and multi-frequency tympanometry were collected using GSI-61 audiometers and GSI-33 middle ear analyzers that were calibrated to American National Standards Institute (ANSI) standards S3.6-2004 and S3.39-2002, respectively. The same make and model of

Table 2

Number of participants and ears from each group included in measurements

Measurement	Number of Participants Included	Number of Ears Included
Audiometric thresholds 226-Hz tympanometry 678-Hz tympanometry 1000-Hz tympanometry Resonant frequency	21	38
Middle ear reflex thresholds	19	33
ER measures DPOAE measures	16	28

equipment was used in both locations for these measures. Additionally, daily calibration of the GSI-33 Middle Ear Analyzers was conducted using the manufacturer supplied test cavity. Data collected for ER and DPOAE measures were obtained using the same piece of equipment transported between locations. Calibration of the Mimosa ER and DPOAE system was conducted before testing each participant using the manufacturer supplied test cavity.

Audiometric Measures

Pure-tone audiometric testing was performed in a sound-treated booth using a standard diagnostic audiometer (Grason-Stadler, GSI-61). Pure-tone air-conduction (AC) thresholds were established using insert earphones (Ear Tone ER-3A) in each ear at 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000, and 8000 Hz. Masked pure-tone bone-conduction (BC) thresholds were measured at 500, 1000, 2000, and 4000 Hz. Due to the disparity across previous studies regarding the definition of hearing loss, prevalence of hearing loss was determined using three criteria. Hearing loss was defined as the presence of hearing thresholds at two or more frequencies in the tested ear at several thresholds levels: (1) greater than 15 dB HL, (2) greater than 20 dB HL, or (3) greater than 25 dB HL. A conductive component was defined as the presence of an air-bone gap of greater than 10 dB HL at two or more frequencies in the tested ear. Hearing loss degree was categorized using the following criteria: mild at 26 to 40 dB HL; moderate at 41 to 55 dB HL; moderately-severe at 56 to 70 dB HL; severe at 71 to 90 dB HL; and profound at > 90 dB HL (Clarke, 1981). When the cutoff for the presence of hearing loss was 15 or 20 dB HL, an additional category of “slight” hearing loss was included, with a range of 16-25 dB HL when the criterion

was 15 dB HL and a range of 21-25 dB HL when the criterion was 20 dB HL. The speech recognition threshold (SRT) was measured using spondees presented via monitored live voice. The SRT was compared to the 3-frequency pure-tone average obtained at 500, 1000, and 2000 Hz in order to verify validity of audiometric results. Word recognition scores were measured as percent correct using Northwestern University-6 (NU6) word lists. The 25 word-lists were presented using monitored live voice at 40 dB SL re: SRT. Word recognition scores were obtained following standard clinical procedures conducted at the NIH and completed to provide participants with a comprehensive audiological evaluation. This measure was not examined in data analyses.

Standard Immittance

Standard immittance measurements were obtained using the Grason Stadler (GSI-33) middle-ear analyzer. Single-frequency admittance tympanograms were measured using a 226-Hz probe tone to obtain tympanic peak pressure (TPP), ear canal volume, and peak-compensated static admittance. Tympanometry was considered normal if the static admittance value was between 0.3-1.7 mmhos (Margolis & Goycoolea, 1993) and if the TPP was between +50 to -150 daPa. The TPP criteria used were a conservative measure in comparison to the Jerger tympanometric classification system, which classifies negative pressure at -200 daPa (Jerger, 1970). Tympanometric width was considered normal between 50-115 daPa (Margolis & Heller, 1987). The TPP obtained from the 226 tympanogram was used as a selection criterion such that only individuals with TPP ± 10 daPa were included in the participant pool for ER and DPOAE measurements. Ear canal volume

measurements assisted in confirming otoscopic findings by verifying an intact tympanic membrane and an unoccluded ear canal.

Acoustic reflex thresholds were determined at 500, 1000, and 2000 Hz in the ipsilateral and contralateral stimulus conditions. Acoustic reflex adaptation was evaluated in the contralateral condition using a 10 second tonal presentation at 500 and 1000 Hz at a level 10 dB above the acoustic reflex thresholds. Presentation levels did not exceed 110 dB HL for either of these tests. Acoustic reflex threshold testing assesses the function of the middle ear system, the inner ear, and the auditory neural pathway by measuring a reflexive contraction of the stapedius muscle in the middle ear in response to loud sounds. Acoustic reflex adaptation was assessed to differentiate a cochlear hearing loss from a retrocochlear hearing loss should a participant present with a sensorineural hearing loss.

Multi-frequency Tympanometry

Additional single frequency tympanograms were obtained using 678- and 1000-Hz probe tones. Susceptance (B) and conductance (G) tympanograms were obtained to provide information about the mass and compliance of the middle ear system. The shape of the tympanograms was evaluated using the Vanhuyse et al. (1975) model. Notching (“W”) of the tympanograms occurs when the middle ear system becomes mass controlled (Margolis et al., 1985). The admittance at +200 daPa and at the central maxima or minima were measured from the B and G tympanograms and compared between participant groups for the 678- and 1000-Hz tympanograms. Using the formulae described by Calandruccio et al. (2006), the admittance at +200 daPa was calculated using Equation 1, and middle ear admittance

at the mid-point was calculated using Equation 2, where Y equals admittance, B equals susceptance, and G equals conductance in mmhos.

$$Y_{+200} = \sqrt{(B_{tail}^2 + G_{tail}^2)} \quad (1)$$

$$Y_{midpt} = \sqrt{[(B_{midpoint} - B_{tail})^2 + (G_{midpoint} - G_{tail})^2]} \quad (2)$$

Middle ear resonant frequency was also obtained using a sequential frequency sweep from 226-2000 Hz in 50 Hz increments. The resonant frequency was automatically calculated by the GSI-33 Middle Ear Analyzer as the frequency where the difference in susceptance from the extreme positive canal pressure to the midpoint peak/dip was equal to 0 mmhos.

ER and DPOAE Measures

Equipment. ER was measured using the commercially available Reflectance Measurement System (Mimosa Acoustics, Inc.) and Mimosa Acoustics RMS 3.1.8 version software. The Mimosa Acoustics Inc. wideband middle ear power analyzer (wbMEPA) plots the ER characteristics of sound transmission by the middle ear. The system uses the four-cavity method of measurement developed by Allen (1985) and used by Keefe et al. (1992) and Voss and Allen (1994). The instrumentation consists of a laptop computer (Dell Pentium laptop), a PC card (PCMCIA card) for digital signal processing, a DPOAE probe system (Etymotic Research ER-10C), an adaptor cable, and a four-cavity calibration device. The PC card is inserted into the computer, which is then connected to the adaptor cable and probe.

Calibration and Measurement. Two separate calibration procedures were conducted prior to data collection from each participant: calibration in the cavity, and calibration of in-the-ear sound pressure. The cavity calibration was made with the probe tip placed in a four-chambered test cavity provided by the manufacturer. This test cavity was used to assess the pressure-frequency response by presenting a 1-sec chirp. The Thevenin equivalent parameters were computed from the probe responses. A pass/fail criterion predetermined by the manufacturer calculates the tolerance range from these measures, based on Thevenin principles (Allen, 1985). The measurements from the four-cavity calibration were used to create a frequency response that was used to obtain the transducer source pressure and source impedance. The second type of calibration was the *in situ* calibration measurement. This calibration measures the pressure-frequency response in the test ear by presenting a 1000 Hz tone at 60 dB SPL and helps to ensure an appropriate probe fit. Both calibration methods were conducted immediately prior to data collection from each participant. All measurements were conducted at ambient pressure; therefore, it was essential that participants have a TPP ± 10 daPa of ambient pressure.

ER represents the proportion of the acoustic signal that is reflected back into the ear canal and is proportional to the amount of power absorbed by the middle ear: power absorption = $1 - ER$ (Feeney, 2005). The Mimosa system represents ER as a percentage.

ER was measured by presenting a chirp signal. A foam tip was placed on the ER-10C probe. Following calibration in the test cavity, the probe was inserted in the participant's ear canal with full insertion depth (approximately 10 mm depending

upon ear canal size and shape) as determined by visual confirmation that the lateral end of the foam tip was flush with the entrance to the external auditory meatus. Once the probe fit had been confirmed by *in situ* ear canal pressure measurement, the chirps were presented at the default level of 60 dB SPL for a 2 sec duration. The chirp level and duration were selected to ensure a sufficient signal-to-noise ratio and an accurate and repeatable response. In accordance with previous reports (Feeney et al., 2003; Feeney & Sanford, 2004), ER measures were repeated three times per ear. These three measurements were averaged at each test frequency to provide the final data set for each ear. The system uses a sampling rate of 48,000 Hz and a maximum frequency range extending from approximately 200-6000 Hz. Two-hundred-forty-eight data points at approximately 20 Hz increments ranging from 211-6000 Hz are recorded and can be exported to a text file.

The Mimosa Acoustic Inc. Hear ID 3.1.8 system was also used to obtain 2f1-f2 DPOAE levels by recording a screening “DP-Gram.” DPOAEs were measured using the same probe fit used for ER recordings. The two stimulus tones were presented at 65 and 55 dB SPL, respectively. The frequencies of the higher tone (f2) were 2000, 3000, 4000 Hz with the lower frequency tone (f1) set such that f2/f1 equaled approximately 1.2. A pass criteria were automatically generated by the system based on the following default settings: DPOAE level was ≥ 10 dB SPL and the difference between the DPOAE level and the noise floor was ≥ 6 dB at each test frequency.

Preliminary Data

Preliminary data were collected to ensure location differences and test order for tympanometry and ER did not affect test results.

Location Differences. Preliminary data were collected to ensure that the test results were similar between locations, and that transporting the Mimosa Reflectance equipment did not affect measured results. Additionally, these measures ensured that the test-retest reliability of the ER system was consistent with previous results (Hunter, 2004; Vander Werff & Prieve, 2004). Data from a pilot group of five normal hearing young female adults without RA (aged 24-31) were collected to compare measurements obtained at each location. All participants had the following tests conducted in both locations and the test order was the same in each location: otoscopy, standard immittance, multi-frequency tympanometry, SRT, air- and bone-conduction thresholds, ER and DPOAEs. This pilot study used the same pieces of equipment that were used throughout the study for data collection. These individuals did not have a significant history of middle ear pathology or surgery, noise exposure, or the use of ototoxic medications. All individuals had hearing sensitivity less than or equal to 15 dB HL with no air-bone gaps > 5 dB present at audiometric test frequencies. All individuals had TPP \pm 10 daPa as measured by 226-Hz tympanometry. One individual had scarring bilaterally on the tympanic membrane as identified through routine otoscopy and another individual had absent contralateral reflexes and a history of head injuries. The inclusion of these individuals was important to ensure the consistency of the equipment between locations for normal as well as abnormal middle ear systems. Both ears were tested, for a total of 10 ears.

The first ear tested was randomized. All measurements for a given individual were conducted on the same day in both locations. ER measures were repeated three times with the same probe fit, and the mean was obtained and used as the final data set. Two sets of measurements with the probe removed and reinserted in between were obtained at each location to ensure the differences between locations did not vary more than expected test-re-test reliability from a different probe fit.

Test Order. In previous research, ER was measured after a 226-Hz tympanogram had been obtained (Feeney et al., 2003; Feeney & Sanford, 2004). A preliminary study involving 10 adult females was conducted to assess whether test order impacts ER measurements and to ensure that the transient pressure manipulation in the ear canal during tympanometry did not alter ER results. Inclusion criteria for this pilot study were a normal tympanogram with peak pressure ± 10 daPa. One ear was randomly chosen from each participant. Each participant had one ER measurement recorded, followed by a 226-Hz tympanogram, and then a subsequent ER measurement.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences Software (SPSS), version 14.0 and Microsoft Excel. Preliminary data compared location differences and test order differences. Analyses of the differences between the RA and NC groups were performed using t-tests and two-way ANOVAs. Most ANOVA results violated Mauchley's test for sphericity. In these cases, the Greenhouse-Geisser correction factor was applied for the degrees of freedom (Greenhouse & Geisser, 1959). The only measures that did not violate sphericity

were bone-conduction thresholds in the preliminary data comparing locations, and DPOAE amplitudes in the results comparing RA and NC groups. ER data were examined in one-third octave frequency intervals ranging from 250-6000 Hz. Previous studies reported ER results in one-third octave frequency intervals (Keefe et al., 1993, Voss & Allen, 1994). Shahnaz and Bork (2006) reported that all significant findings observed when comparing 248 frequencies were replicated using one-third octave intervals. All tests were two-sided and p-values < 0.05 were considered statistically significant.

Chapter 5: Results

Preliminary Data: Location Differences

Statistical analysis was completed using repeated measures ANOVAs and repeated measures *t*-tests. A 2 x 15 (location x frequency) ANOVA with repeated measures on both factors indicated no significant differences between locations, $F(1, 9) = 2.82, p = 0.13$. Main effect of frequency and interactions could not be calculated due to the low degrees of freedom. The mean difference between locations was < 1% ER across frequencies (differences ranged from -4.1% to 2.3% ER) and the mean difference in standard deviations between locations was 0.76 across the frequency range (ranged from -4.1 to 2.3). The comparisons between the mean ER data are displayed in Figures 8 and 9.

A 2 X 15 (test x frequency) ANOVA with repeated measures on both factors indicated no significant differences between test-retest measurements, $F(1, 9) = 1.987, p = 0.32$. Main effect of frequency and interactions could not be calculated due to the low degrees of freedom. The average difference between the first and second run within individuals using a different probe fit at the same location was 0.15% ($\pm 1.5 SD$) at the National Institutes of Health, and 0.42% ($\pm -2.06 SD$) at University of Maryland, College Park. The comparisons between the test-retest of different probe fits recorded at the National Institutes of Health are displayed in Figure 10. Comparable findings were found at the University of Maryland, College Park and are not shown. ER measurements in this sample of young normal adults were comparable to existing normative data (Feeney et al., 2002; Keefe et al., 2003; Margolis et al., 1999; Shahnaz & Bork, 2006).

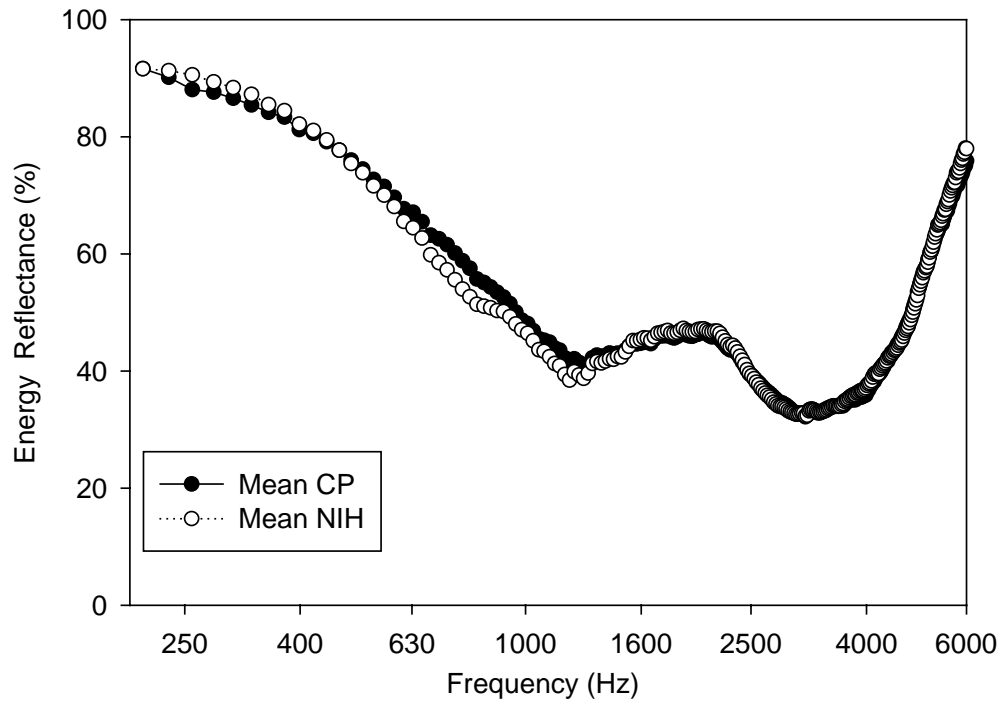


Figure 8. Mean ER plotted as a function of frequency (N = 10 ears) compared between locations.

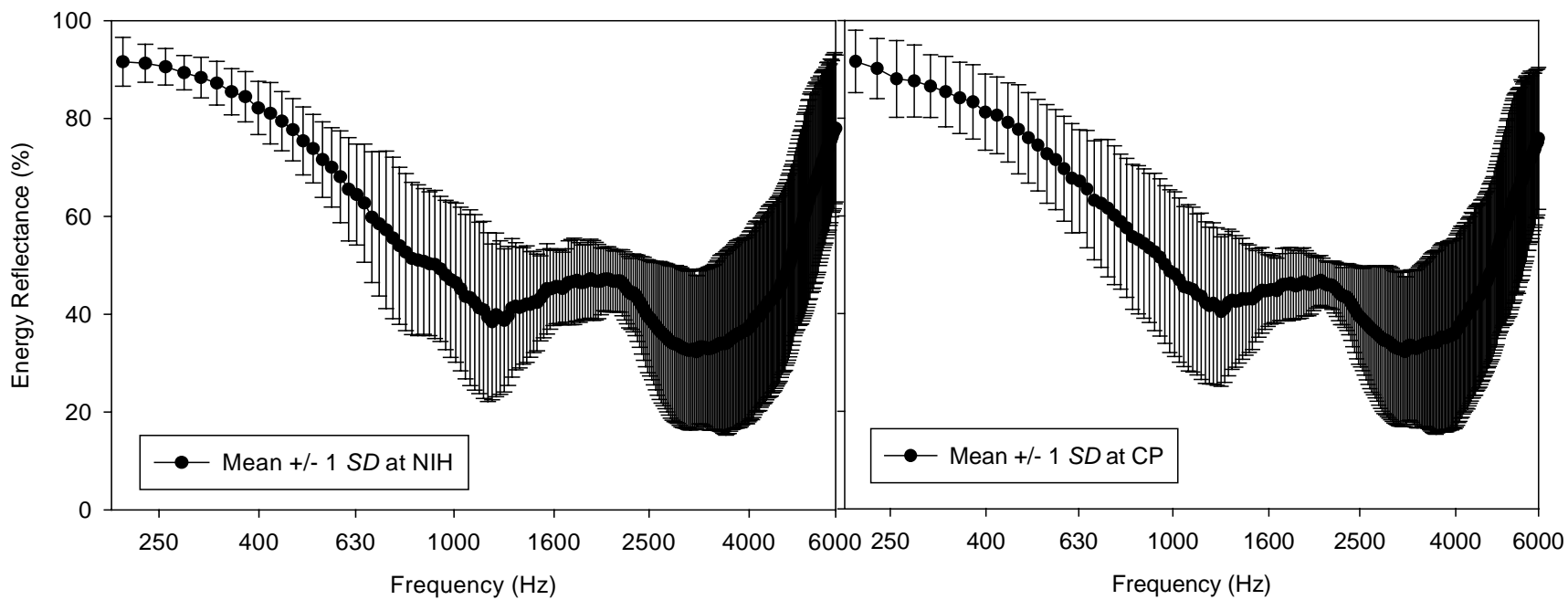


Figure 9. Mean ER plotted as a function of frequency (N = 10 ears) with error bars representing ± 1 SD from the mean, compared between locations: University of Maryland, College Park (CP) (right panel) and the National Institutes of Health (NIH) (left panel).

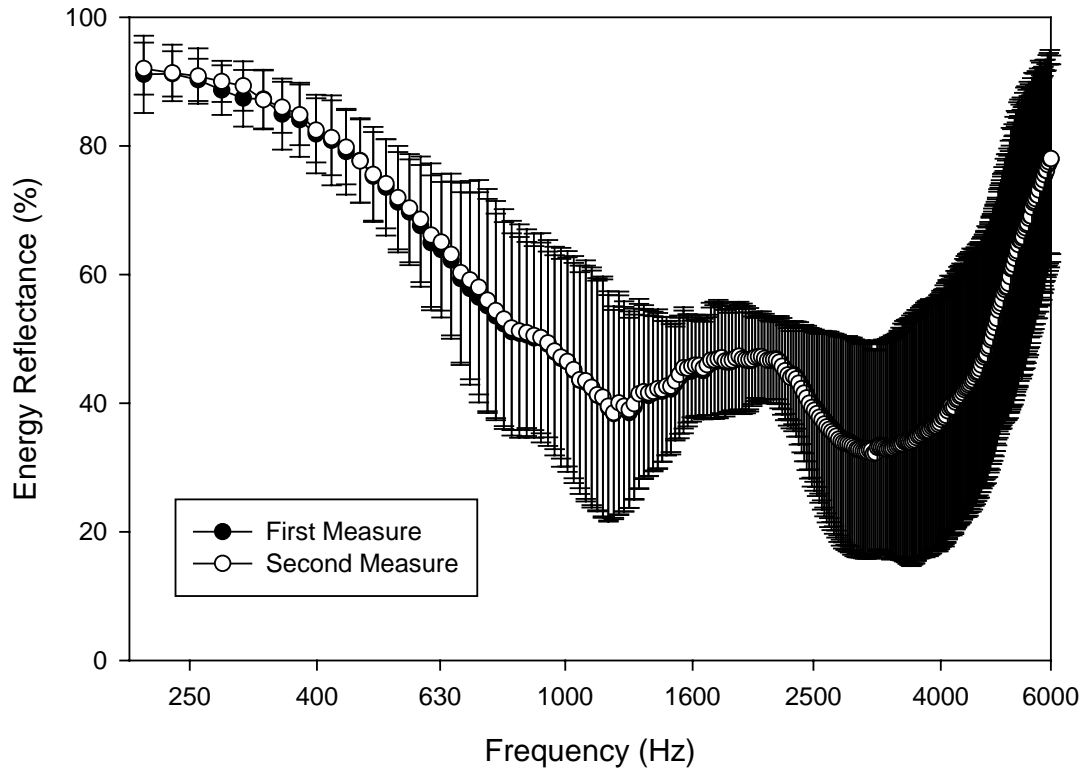


Figure 10. Test-retest measurements obtained at National Institutes of Health. Mean ER plotted as a function of frequency ($N = 10$ ears) with error bars representing ± 1 *SD* from the mean, compared between first (closed symbols) and second (open symbols) test measures within individuals.

Audiometric and immittance measures were consistent between locations. Air- and bone-conduction threshold differences between locations were all within ± 5 dB for each test frequency, which is consistent with expected test-retest reliability. A 2×9 (location \times frequency) ANOVA with repeated measures on both factors indicated no significant differences in air conduction thresholds between locations, $F(1, 9) = 0.03, p = 0.81$. Main effect of frequency and interactions could not be calculated due to the low degrees of freedom. A 2×4 (location \times frequency) ANOVA with repeated measures on both factors indicated no significant differences in bone-conduction thresholds between locations, $F(1, 9) = 3.45, p = 0.10$. Main effect of frequency and interactions could not be calculated due to the low degrees of freedom. A 2×3 (location \times frequency) ANOVA with repeated measures on both factors indicated no significant differences in DPOAE level between locations, $F(1, 9) = 2.19, p = 0.17$. Main effect of frequency and interactions could not be calculated due to the low degrees of freedom. All individuals passed the DPOAE screening criteria at both locations.

Identical values were obtained for 226-Hz static admittance between locations and, therefore, static admittance was not significantly different between locations ($t = 0.0, p = 1.0$). There were no statistically significant differences in TPP ($t = -0.56, p = 0.59$). TPP was within ± 10 daPa for all individuals at both locations, with an average difference of 5 daPa between locations and a difference range of 0 – 10 daPa ($SD = 4.7$). Multifrequency tympanometry maintained identical qualitative shapes (notched versus single peaked) between locations. Static admittance values for 678- and 1000-Hz tympanograms were not significantly different between locations ($t =$

1.96, $p = 0.08$; $t = 1.80$, $p = 0.10$, respectively). The mean difference for static admittance values of a 678-Hz admittance tympanogram was 0.14 mmhos ($SD = 0.18$) and a 1000-Hz admittance tympanogram was 0.18 ml ($SD = 0.16$). There were no significant differences between locations ($t = -1.08$, $p = 0.31$). The average difference in resonant frequency values between locations was 40 Hz, with a range of 0-100 ($SD = 45.9$). The mean resonant frequency was 1070 Hz ($SD = 170$) at the National Institutes of Health and 1090 ($SD = 151$) at the University of Maryland, College Park. Based on these results, which revealed no statistical differences between locations, testing was conducted at two locations.

Preliminary Data: Test Order

All participants had normal 226-Hz tympanograms with a single peak, normal static admittance values (range 0.4-1.1 ml), and normal TPP (± 10 daPa). Mean ER data and mean ER ± 1 SD for each test condition are shown in Figures 11 and 12, respectively. A 2 x 15 (test x frequency) ANOVA with repeated measures on both factors indicated no significant differences between pre- and post-tympanometry ER measurements, $F(1, 9) = 0.04$, $p = 0.85$. Main effect of frequency and interactions could not be calculated due to the low degrees of freedom. Based on this preliminary finding, the order of testing was not varied and ER was performed following tympanometry.

Audiometric Measures

The prevalence of hearing impairment did not significantly differ between participants with RA and those without the disease. As stated previously, for

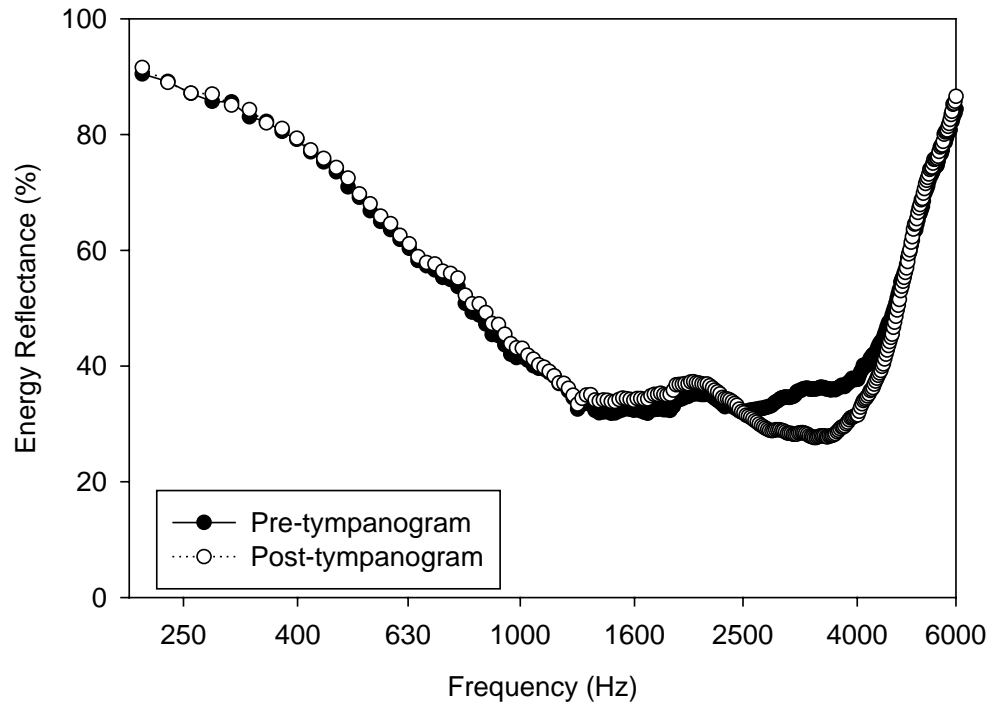


Figure 11. Mean ER plotted as a function of frequency (N = 10 ears) compared between measurements obtained before (closed symbols) and after a 226-Hz tympanogram (open symbols).

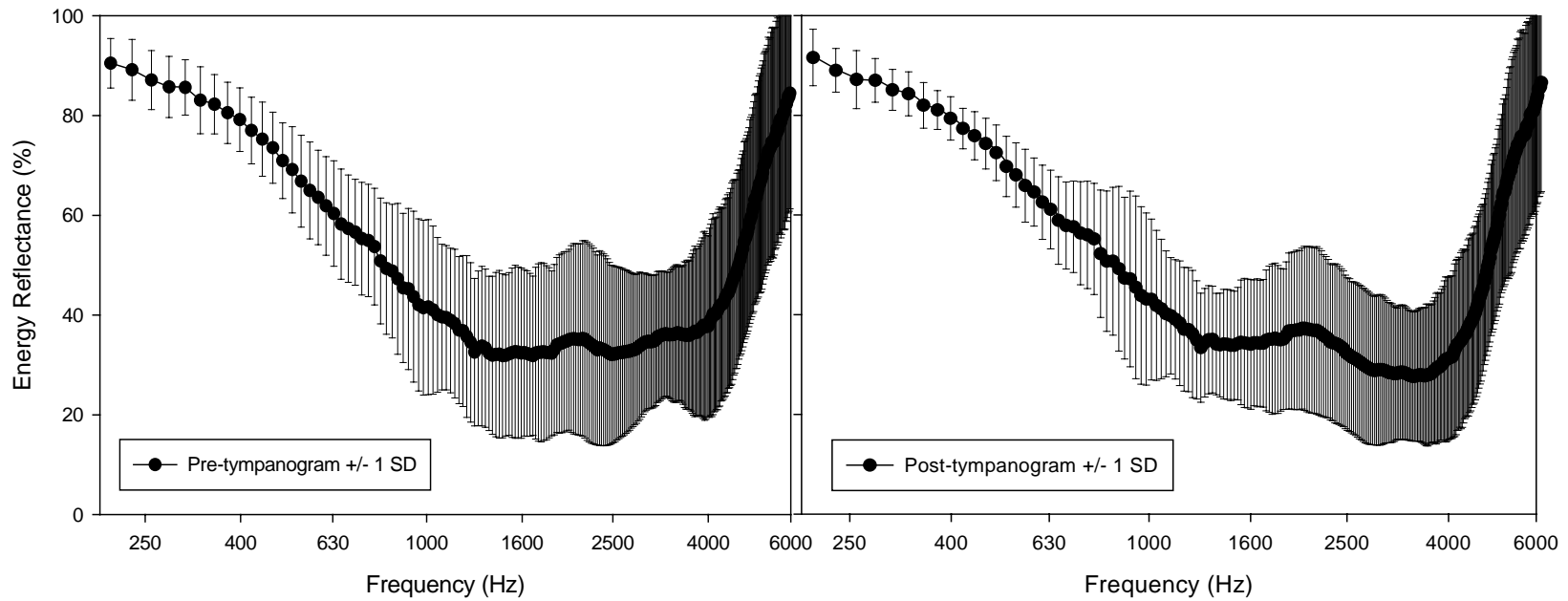


Figure 12. Mean ER plotted as a function of frequency (N = 10 ears) with error bars representing ± 1 SD from the mean, compared between measurements obtained before (left panel) and after (right panel) a 226-Hz tympanogram.

comparisons with previous literature, three different criteria were used to define hearing loss, and prevalence of hearing loss was determined for each group using each of the three criteria. Hearing loss was defined as the presence of hearing thresholds at two or more frequencies in the tested ear that were (1) greater than 15 dB HL, (2) greater than 20 dB HL, or (3) greater than 25 dB HL. Table 3 lists the number of ears and participants in each group that presented with hearing loss for each of the three criteria. A conductive component was defined as the presence of an air-bone gap of greater than 10 dB HL at two or more frequencies in the tested ear. A chi-square test of independence comparing the presence or absence of hearing loss was not significantly different between groups for any of the three hearing loss criteria: greater than 15 dB HL, $\chi^2(1, N = 38) = 0.10$ ($p > 0.05$); greater than 20 dB HL, $\chi^2(1, N = 38) = 0.0$ ($p > 0.05$); or greater than 25 dB HL, $\chi^2(1, N = 38) = 0.47$ ($p > 0.05$). No individuals in either group presented with a conductive or mixed type of hearing loss.

Based on this study's criterion for hearing loss at greater than 20 dB HL, eight individuals in the RA group presented with sensorineural hearing loss: seven were bilateral and one was unilateral. Two of the individuals were male, ages 59 and 60 years, and six were female, ages 42, 47, 57, 59, 61 and 63 years, with a mean age of 56 years ($SD = 7.4$ years). Hearing loss was generally found in the high-frequencies and the degree varied across individuals: six had a mild hearing loss, one had a moderate hearing loss, and one had a severe hearing loss. In the NC group, eight individuals presented with sensorineural hearing loss. Two were male, ages 60 and 63 years, and six were female, ages 56, 58, 59, 60, 63 and 63 years, with a mean age

Table 3

Comparisons of Hearing Loss at Different Threshold Classifications

Group	> 15 dB HL Ears; Participants	> 20 dB HL Ears; Participants	> 25 dB HL Ears; Participants
RA	23; 13	15; 8	9; 5
NC	21; 12	15; 8	13; 7

Note. Hearing loss was defined as the presence thresholds poorer than the threshold criterion at two or more frequencies in a given ear.

60.25 years ($SD = 2.6$ years). The mean age of participants with hearing loss was not significantly different between groups ($t = 1.53$; $p = .15$). In the NC group, all of the affected participants had bilateral hearing losses. However, one individual had one ear excluded due to scarring on the tympanic membrane and a significant otologic history for ear infections in that ear. Therefore, in total, there were 15 ears with hearing loss in the NC group included in data analysis. Most individuals presented with a mild to moderate high-frequency hearing loss with elevated thresholds at 6000 and 8000 Hz. The number and percentage of individuals with hearing loss (8/21; 38%) and the number and percentage of ears with hearing loss (15/38; 39%) were the same in both the RA and NC groups. By comparing different hearing loss threshold level classifications between groups, the lower threshold (greater than 15 dB HL) included hearing losses which were typically a slight high-frequency sensorineural hearing loss. Similarly, the more stringent criteria (greater than 25 dB HL) eliminated individuals with mild high-frequency hearing loss. Despite the varying criteria, the prevalence of hearing loss was comparable between groups.

A 2 x 10 (group x frequency) ANOVA with repeated measures on the second factor was used to compare the mean air-conduction thresholds between groups. Figure 13 illustrates mean air-conduction thresholds for both groups. Air-conduction thresholds were not significantly different between groups, $F(1, 74) = 1.87$, $p = 0.18$. As might be expected, a significant effect of frequency was found for air-conduction thresholds, $F(2, 154) = 19.41$, $p = 0.0001$. There was not a significant interaction between group and frequency for air-conduction thresholds, $F(2, 154) = 1.89$, $p = 0.15$. Pairwise comparisons of frequency revealed significant differences ($p < 0.05$)

for high-frequencies in air-conduction thresholds compared to lower- and mid-frequencies. Air-conduction frequencies at 6000 and 8000 Hz were significantly worse than all other frequencies, and 8000 Hz was worse than 6000 Hz.

A 2 x 4 (group x frequency) ANOVA with repeated measures on the second factor was used to compare the mean bone-conduction thresholds between groups. Bone-conduction thresholds were not significantly different between groups, $F(1, 74) = 1.02, p = 0.32$. There was a significant effect of frequency, $F(2, 135) = 10.01, p = 0.0001$, and a significant interaction between group and frequency for bone-conduction thresholds, $F(2, 135) = 4.11, p = 0.02$. Pairwise comparisons of frequency revealed significant differences ($p < 0.05$) for high-frequencies in bone-conduction thresholds. Bone-conduction thresholds at 4000 Hz were significantly worse than at all other frequencies. This was expected due to the presence of high frequency hearing loss. The mean and standard deviation values for bone-conduction thresholds are shown in Table 4.

A 2 x 4 (group x frequency) ANOVA with repeated measures on the second factor was used to compare air-bone gaps between groups. There was not a significant difference between groups, $F(1, 74) = 3.71, p = 0.06$. A significant effect of frequency was found, $F(3, 200) = 2.89, p = 0.04$. However, pairwise frequency comparisons were not significant at $p < 0.05$ level. There was not a significant interaction between group and frequency, $F(3, 200) = 1.57, p = 0.20$. Table 5 displays comparisons between groups across frequencies.

In the present study, 38% of the ears from both the RA group and NC group had hearing loss, defined as air-conduction thresholds poorer than 20 dB HL at two or

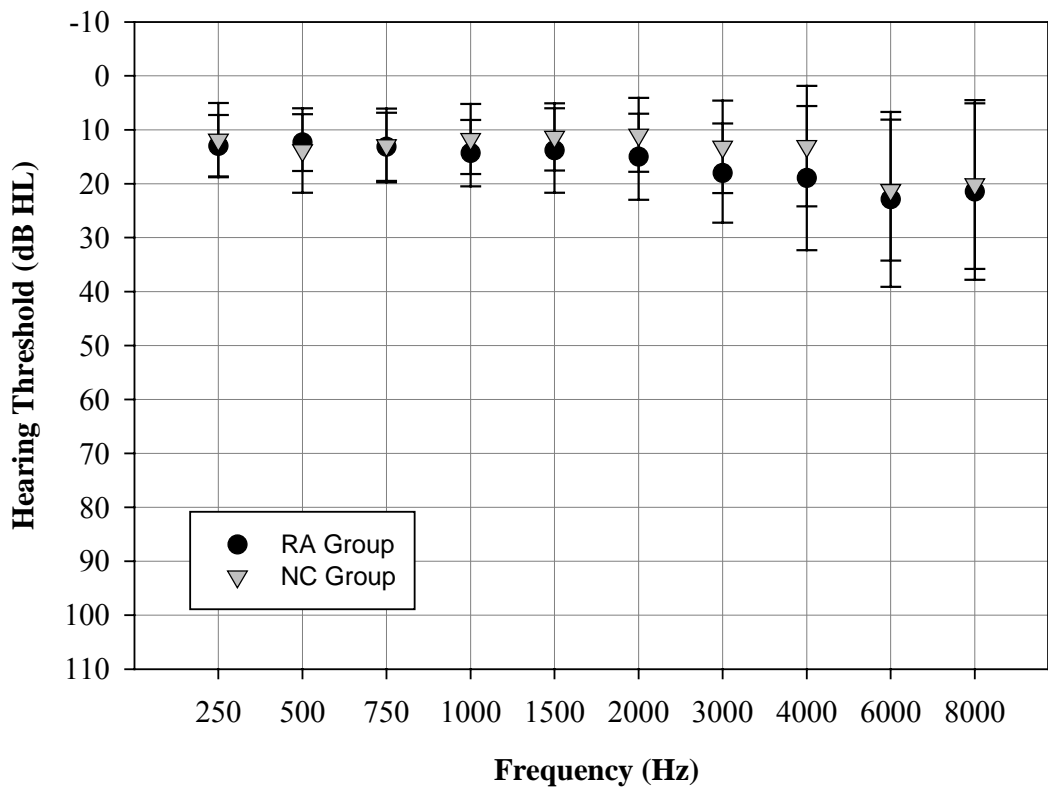


Figure 13. Mean air-conduction thresholds compared between RA (filled circles) and NC (shaded triangles) groups (N = 38 ears per group). Error bars represent ± 1 SD from the mean. No significant differences were found between groups ($p > 0.05$).

Table 4

Mean Bone-Conduction Thresholds Compared Between Groups

Frequency (Hz)	RA Group (dB HL) <i>M</i> (\pm <i>SD</i>)	NC Group (dB HL) <i>M</i> (\pm <i>SD</i>)
500	10.5 \pm 4.7	13.6 \pm 8.4
1000	12.2 \pm 5.9	10.5 \pm 7.1
2000	14.9 \pm 7.8	10.9 \pm 6.4
4000	18.4 \pm 14.1	15.3 \pm 10.3

Note. There were no significant differences between groups ($p > 0.05$).

Table 5

Mean Air-Bone Gap Differences Compared Between Groups

Frequency (Hz)	RA Group (dB HL) <i>M</i> (\pm <i>SD</i>)	NC Group (dB HL) <i>M</i> (\pm <i>SD</i>)
500	2.11 \pm 3.42	1.32 \pm 2.77
1000	2.37 \pm 3.23	1.71 \pm 3.14
2000	1.05 \pm 2.07	1.18 \pm 2.15
4000	1.84 \pm 2.71	0.26 \pm 1.13

Note. There were no significant differences between groups ($p > 0.05$).

more frequencies. However, this definition does not account for an expected decrease in hearing that is associated with age and, therefore, comparisons were made with existing normative data for hearing thresholds based on age and gender. Figure 14 shows the air-conduction thresholds for each ear tested in both groups as a function of age. The dashed and solid gray lines represent the 50th and 95th percentiles, respectively, based on normative data collected by Morrell, Gordon-Salant, Pearson, Brant, and Fozard (1996) at frequencies between 500-4000 Hz, and standards reported by the International Organization for Standardization for 8000 Hz (ISO, 1984).

The number of thresholds across frequencies that were poorer than the 95th percentile (ISO 1984; Morrell et al., 1996) are shown in Table 6. The three-frequency PTA was included in the table for comparison, but was not included in totals or statistical analysis due to its duplicative nature with the 500, 1000 and 2000 Hz discrete frequency comparisons. A chi-square test of independence using nominal categorical variables of the presence or absence of hearing thresholds that were poorer than the 95th percentile revealed a significant difference between groups at the $p < 0.001$ level, $\chi^2(1, N = 190) = 15.75$. Analysis included results for both genders for 500, 1000, 2000, 4000, and 8000 Hz. A greater number of thresholds from those participants with RA were poorer than the 95th percentile across the test frequencies.

Standard Immittance

Middle ear measurements were classified as normal or abnormal, as determined by comparisons to existing normative values (Margolis & Goycoolea,

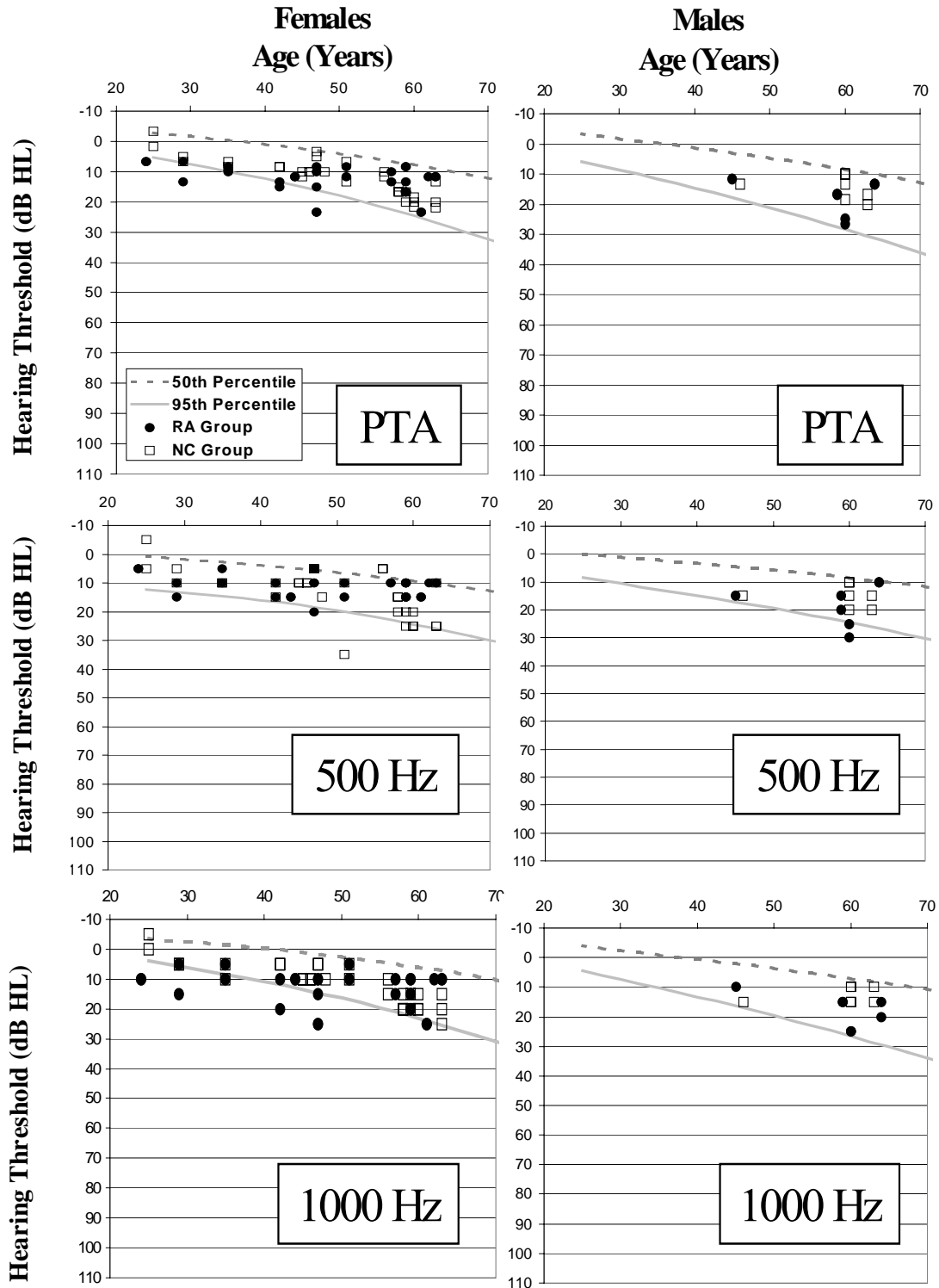


Figure 14. Air conduction thresholds for two groups as a function of age at six different frequencies, with comparison to normative data from Morrell et al. (1996) for frequencies between 500 – 4000 Hz and from ISO (1984) for 8000 Hz.

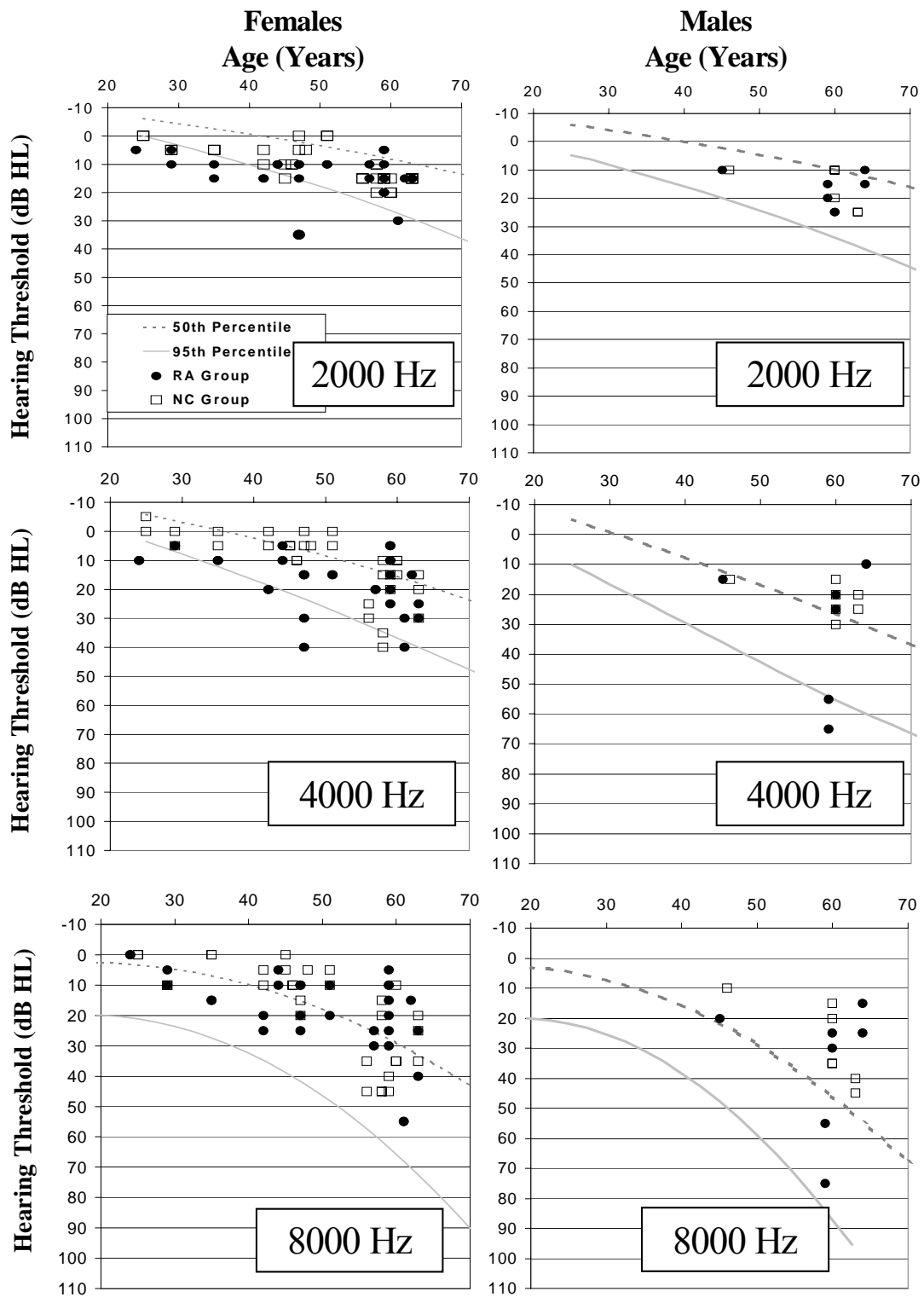


Figure 14. Air conduction thresholds for two groups as a function of age, continued.

Table 6

*Number of Ears with Air-Conduction Thresholds Poorer than the 95th Percentile
Compared to Normative Data Based on Age and Gender*

Frequency (Hz)	Females		Males	
	RA	NC	RA	NC
3-Frequency PTA	6	0	0	0
500	2	4	2	0
1000	10	1	0	0
2000	12	3	0	0
4000	7	2	2	0
8000	0	0	0	0
Totals (500-8000 Hz):	31	10	4	0

Note. A significant difference between groups was found ($p < 0.001$) for the total number of thresholds poorer than the 95th percentile at 500-8000 Hz.

1993; Margolis & Heller, 1987). Mean peak compensated static admittance and ear canal volume obtained from the 226-Hz tympanograms are listed for both groups in Table 7. Neither measure was significantly different between groups: static admittance ($t = 0.80, p = 0.42$); ear canal volume ($t = 0.08, p = 0.94$). Two ears from the same individual in the RA group had abnormally high static admittance values (great than 1.7 mmhos) and no ears had low static admittance (less than 0.3) compared to normative data (Margolis & Goycoolea, 1993). No individuals from the NC group had a static admittance value outside this normative range (0.3 – 1.7 mmhos). The TPP was significantly different between groups ($t = -3.31, p = 0.001$).

All ears of NC participants had a TPP within ± 10 daPa; however, 10/38 ears in the group with RA had TPP not within ± 10 daPa. All TPP measurements included in data analysis were considered clinically normal and were within -150 to $+50$ daPa. Most ears had TPP within -50 to $+50$ daPa. Only one individual had an ear with TPP lower than -100 daPa. Other measurements (e.g., audiometric pure-tone thresholds, resonant frequency etc.) obtained from the individual with TPP = -140 daPa were within ± 1 SD of the group means. While there was a statistically significant difference in TPP between groups, the values were still within clinical normal limits. The TPP could potentially influence the results were ER and DPOAE measures. The equipment used for ER and DPOAE does not compensate for TPP; and, therefore, the 10 ears from the RA group and the corresponding normal control ears were excluded from analyses of the ER and DPOAE data.

Tympanometric width was also recorded; however, due to differences in how the equipment calculated the tympanometric width in the NC group, accurate

Table 7

226-Hz Tympanometric Static Admittance (Y), Ear Canal Volume (ECV), and Tympanometric Peak Pressure (TPP) Measurements Compared Between Groups

Measure	RA			NC		
	Mean	SD	Range	Mean	SD	Range
Y (mmhos)	0.92	0.81	0.4-4.8	0.81	0.31	0.4-1.5
ECV (cm ³)	1.41	0.33	0.7-2.1	1.40	0.26	1.0-1.9
TPP (daPa)*	-15.0	29.43	(-140)-(+30)	1.32	5.16	(-10)-(+10)

Note. The asterisk denotes (*) a statistically significant difference at $p < 0.05$ level.

comparisons between groups cannot be made¹. The mean tympanometric width in the RA group was 109.34 daPa ($SD = \pm 68.41$). Tympanometric width was abnormal in 20/38 ears in the RA group. Tympanometric width greater than 115 daPa was recorded in 13/38 ears, of which 5/38 were greater than 200 daPa. Tympanometric width less than 50 daPa was recorded in 7/38 ears. Estimates of the NC group tympanometric width revealed no ears had a width greater than 115 daPa, and 5/38 ears had a width less than 50 daPa.

The means and standard deviations for acoustic reflex thresholds (ARTs) obtained from each group are listed in Table 8. Thirty-three ears from each group were included in the analysis. A 2 x 6 (group x frequency) ANOVA with repeated measures on the second factor was used to compare the mean ARTs between groups. ARTs were not significantly different between groups, $F(1, 64) = 0.61, p = 0.44$. A significant effect of frequency was found for ARTs, $F(3, 176) = 38.11, p = 0.0001$, and no significant interaction between group and frequency, $F(3, 176) = 0.53, p = 0.64$. Pairwise comparisons of frequency revealed significant differences ($p < 0.05$) between almost all test conditions. Acoustic reflex adaptation was measured when possible (stimulus level ≤ 110 dB HL) at 500 and 1000 Hz in the contralateral test condition. This included 30/38 ears at 500 Hz and 34/38 ears at 1000 Hz in the RA group, and 31/38 at 500 Hz and 31/38 ears at 1000 Hz in the NC group. All individuals tested exhibited negative reflex adaptation.

¹ The GSI-33 Middle Ear analyzer at University of Maryland, College Park (CP) could not automatically calculate tympanometric width. Manual estimates were obtained at CP; however, comparisons between manual calculations and automatic calculations using the GSI-33 at the National Institutes of Health revealed differences of 5 – 10 daPa dependent on the method of calculation. Therefore, automatic and manual calculations of tympanometric width could not be compared between groups.

Table 8

Acoustic Reflex Thresholds Compared Between Groups

Frequency (Hz)	RA		NC	
	Ipsi	Contra	Ipsi	Contra
500 <i>M(SD)</i>	86.21(5.45)	94.10(7.34)	86.97(6.72)	93.79(7.40)
1000 <i>M(SD)</i>	83.94(5.70)	90.91(5.79)	86.21(7.81)	91.97(7.28)
2000 <i>M(SD)</i>	86.82(6.10)	91.36(6.16)	87.88(7.91)	92.73(8.12)

Note. There were no significant differences found between groups ($p > 0.05$).

Multi-frequency Tympanometry

Additional susceptance (B) and conductance (G) tympanograms were obtained using probe tones of 678- and 1000-Hz. In the RA group, 19/38 ears had a notch in the 678-Hz B-tympanogram, compared to 12/38 ears in the NC group. The proportion of notched versus single-peaked tympanograms at 678-Hz was not significantly different between groups using a chi-square test, $\chi^2 (1, N = 38) = 2.67, p > 0.05$. Tympanometric shape patterns were determined using the Vanhuysse model (Vanhuysse et al., 1975). The shape classifications of the 678-Hz probe tone are compared between groups in Figure 15. In the RA group, 19 ears had a 1B1G pattern, 16 ears had a 3B1G pattern, two ears had a 3B3G pattern, and one ear did not follow any patterns with notching occurring at more than one pressure. In the NC group, 26 ears had a 1B1G pattern, and 12 had a 3B1G pattern. Ten ears in the RA group and five ears in the normal control group had a midpoint notch value that was equal to or less than the value of the tail of the tympanogram, indicating a middle ear system that is mass dominated.

Results for a 1000-Hz tympanogram revealed notched B-tympanograms for 35/38 ears in the RA group and 36/38 ears in the normal control group. The proportion of notched versus single-peaked tympanograms at 1000-Hz was not significantly different between groups using a chi-square test, $\chi^2 (1, N = 38) = 2.67, p > 0.05$. Tympanometric shapes for the 1000-Hz probe tone are plotted for each group in Figure 16. Results in the RA group revealed three ears had a 1B1G pattern, 21 ears had a 3B1G pattern, 13 ears had a 3B3G pattern, and one ear that did not follow any

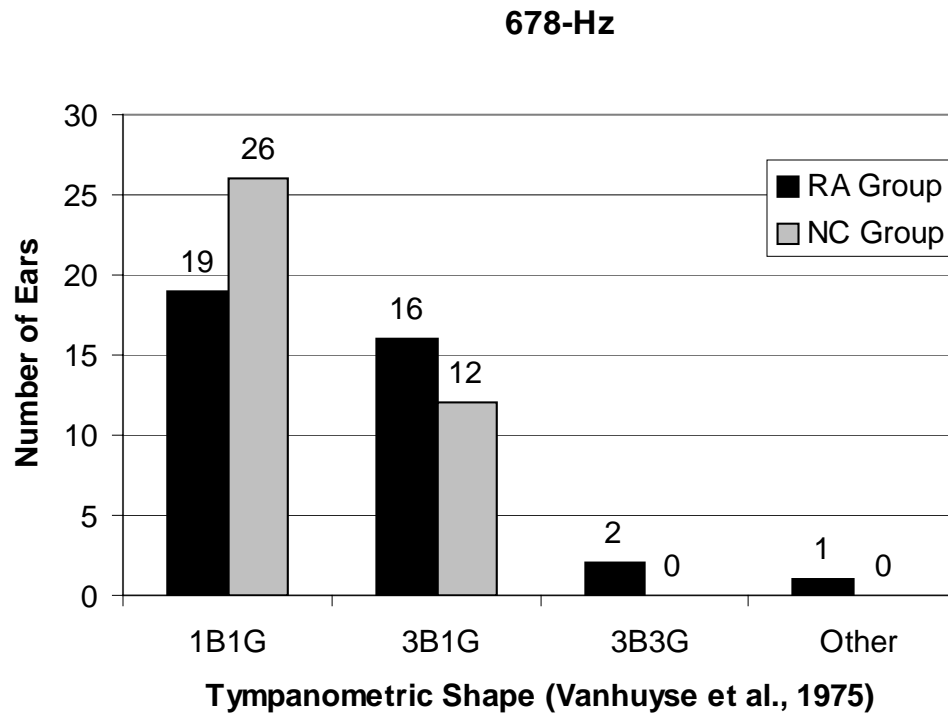


Figure 15. Tympanometric shape obtained for 678-Hz tympanograms by 38 ears in each group, classified according to the Vanhuyse et al. (1975) model.

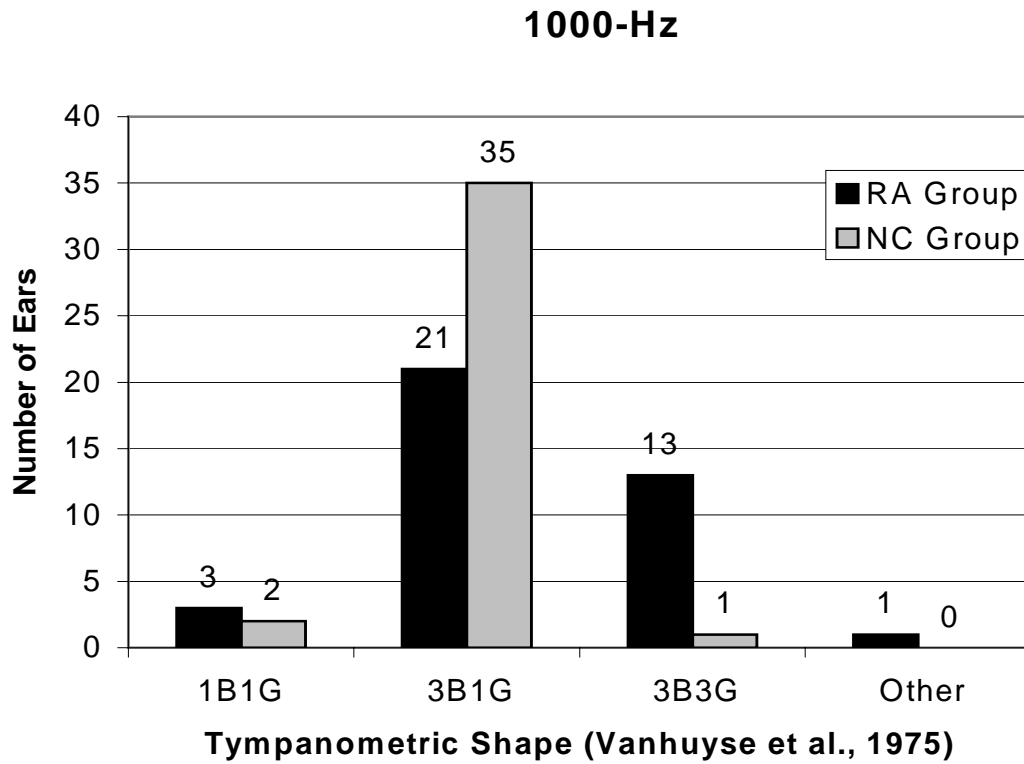


Figure 16. Tympanometric shape obtained for 1000-Hz tympanograms by 38 ears in each group, classified according to the Vanhuysse et al. (1975) model.

patterns with notching occurring at more than one pressure. This was the same individual that had an “other” classification when using a 678-Hz probe tone. In the NC group, two ears were consistent with a 1B1G pattern, 35 were consistent with a 3B1G pattern, and one ear was consistent with a 3B3G pattern. Thirty four of the 38 ears in both the RA group and the NC group had a central notch value that was equal to or less than the value of the tail of the B-tympanogram indicating the middle ear system becoming mass dominated.

Admittance values measured at the positive tails (+200) and midpoints of 678- and 1000-Hz tympanograms were also compared between groups. Data for the two groups are listed in Table 9. Comparisons of mean Y_{midpt} did not significantly differ between groups at 678-Hz ($t = -.96$; $p = 0.34$) or at 1000-Hz ($t = 0.578$; $p = 0.57$). Additionally, there were no statistically significant differences between groups for Y_{+200} at 678-Hz ($t = 0.54$; $p = 0.59$) or at 1000-Hz ($t = 1.54$; $p = 0.13$).

The middle ear resonant frequency was calculated by the GSI-33 middle ear analyzer using a multi-frequency sweep from 200-2000 Hz in 50 Hz steps. The RA group had a significantly lower resonant frequency compared to the NC group ($t = 3.36$, $p < 0.001$). For the RA group, the mean resonant frequency was 790 Hz, the median was 825 Hz, and the range was 250-1150 Hz. For the NC group, the mean resonant frequency was 967 Hz, the median was 950 Hz, and the range was 550-1700 Hz. Figure 17 displays box plots representing the resonant frequency from the 5th to 95th percentiles compared between groups. Valvik et al. (1994) found a 90% range of 650-1500 Hz using comparable equipment and methods for middle ear resonant frequency. In the RA group, nine ears had a resonant frequency below 650 Hz and

Table 9

Admittance Calculations (Y_{+200} and Y_{midpt}) Compared Between Groups at 678- and 1000-Hz Tympanograms

Probe Frequency	RA <i>M (SD)</i>	NC <i>M (SD)</i>
678-Hz		
Y_{+200}	4.01 (0.86)	4.10 (0.68)
Y_{midpt}	3.09 (1.86)	2.74 (1.27)
1000-Hz		
Y_{+200}	6.20 (1.30)	6.66 (1.34)
Y_{midpt}	3.96 (1.93)	4.22 (2.07)

Note. No statistically significant differences were found between groups ($p > 0.05$).

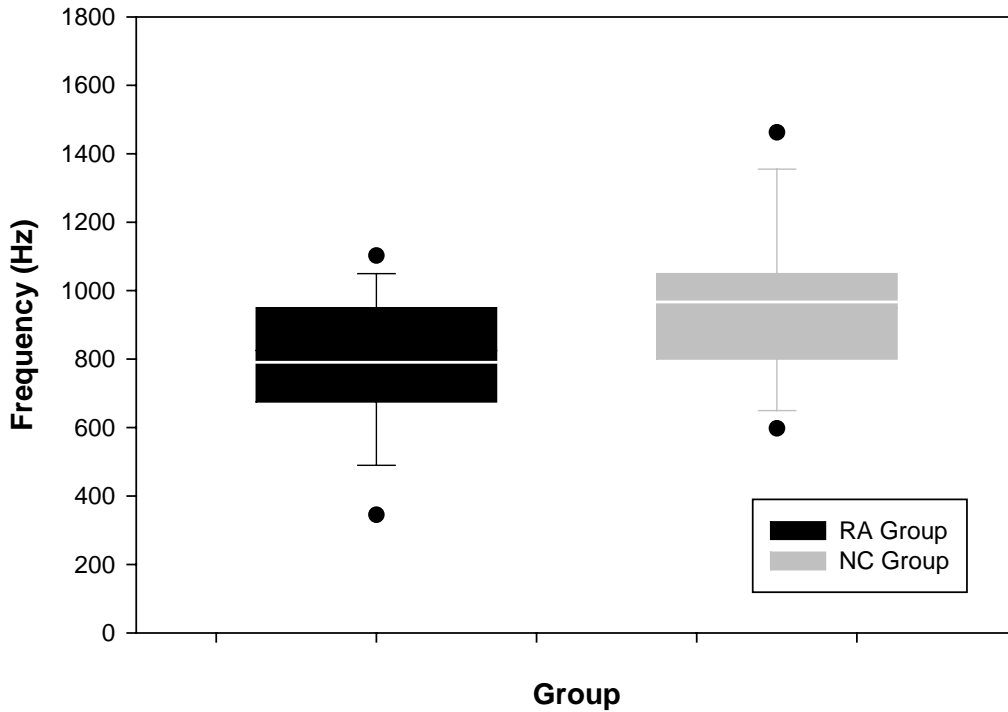


Figure 17. Box plots of middle ear resonant frequencies for the 38 ears in each group. Data are shown in percentiles: the 10th and 90th percentiles are represented by the edges of the boxes and the 25th and 75th percentiles are represented by the error bars. The 5th and 95th percentiles are represented by the dots, and the mean is indicated by the line in the box plot. The RA group had significantly lower resonant frequency ($p < 0.001$).

zero ears above 1500 Hz. In the NC group, two ears had a resonant frequency below 650 Hz and one ear above 1500 Hz. A low resonant frequency is consistent with an increased mass dominance of the middle ear system.

An additional analysis was conducted to ensure the validity of the significant middle ear resonant frequency findings. Valvik et al. (1994) reported that when the susceptance slope is flat close to the point at which susceptance is equal to zero, there may be variable resonant frequency results and poor test-retest within an individual. The outliers for both high and low resonant frequency values in both groups were reviewed, and the individual in the NC group with abnormally high resonant frequency had a flat susceptance slope. Statistics were repeated excluding this NC participant with a resonant frequency of 1700 Hz and excluding the matched participant in the RA group. A statistically significant difference in the resonant frequency was still found between groups ($t = 3.17$; $p = .002$) when these data were excluded.

Tympanometric and pure-tone audiometric results were compared within individuals in the RA group to examine for possible relationships across measurements. These comparisons for 21 participants (38 ears) in the RA group are displayed in Table 10. Static admittance values for 226 Hz tympanograms greater than 1.7 mmhos are listed as “high.” The column representing 678- and 1000-Hz tympanograms lists the shape according to Vanhuyse et al. (1975). Only ears for which notching occurred are listed. No ears had a notched tympanogram at 226-Hz. The resonant frequency was considered low for frequencies less than 650 Hz, and high for frequencies greater than 1500 Hz (Valvik et al., 1994). No individuals in the

Table 10

Comparisons of Tympanometry and Pure-tone Audiometry Measures for Ears of Individuals in the RA Group

Age/Sex	Ear	226-Hz (mmhos)	678-Hz	1000-Hz	Res. Freq. (Hz)	HL > 20 dB HL	HL > Age
24-F	R				1150		yes
24-F	L				1100		yes
29-F	R		3B1G	3B3G	700		yes
29-F	L			3B1G	950		yes
35-F	R		3B1G	3B1G	700		yes
35-F	L		3B1G	3B1G	1000		yes
42-F	R		3B1G	3B1G	750	yes	yes
42-F	L		3B1G	3B3G	850		yes
44-F	R		3B1G	3B3G	700		
44-F	L		3B1G	3B3G	750		
45-M	L		3B1G	3B3G	600 (low)		
47-F	R			3B1G	850		yes
47-F	R			3B3G	800	yes	yes
47-F	L		3B1G	3B3G	600 (low)	yes	yes
47-F	R			3B1G	900		
47-F	L		3B1G	3B1G	900		
51-F	R		3B1G	3B1G	350 (low)		
51-F	L			3B1G	550 (low)		
57-F	R		Other	Other	250 (low)	yes	
57-F	L		3B1G	3B3G	550 (low)	yes	
59-F	R		3B3G	3B3G	850	yes	
59-F	L			3B1G	900	yes	
59-F	R	2.4 (high)	3B1G	3B3G	550 (low)		
59-F	L	4.8 (high)	3B3G	3B3G	400 (low)		
59-F	R			3B1G	500 (low)		
59-F	L			3B1G	1050		
59-F	R			3B1G	900		
59-M	R			3B1G	800	yes	yes
59-M	L			3B1G	800	yes	yes
60-M	R			3B1G	950	yes	yes
60-M	L		3B1G	3B3G	750	yes	yes
61-F	R		3B1G	3B3G	950	yes	yes
61-F	L		3B1G	3B1G	950	yes	yes
62-F	L				1050		
63-F	R			3B1G	800	yes	
63-F	L			3B1G	900	yes	
64-M	R			3B1G	1050		
64-M	L			3B1G	900		

Note. Horizontal lines delineate individuals. “R” represents right ears, and “L” represents left ears.

RA group had a “high” resonant frequency. The multiple middle ear measurements generally are consistent with each other. Individuals with notching at 678-Hz also had notching at 1000-Hz probe tones. Individuals with a low resonant frequency generally had more complex tympanometric shapes.

Table 10 also compares ears with hearing loss at two frequencies greater than 20 dB HL with at least one frequency poorer than the 95th percentile based on age and gender (Morrell et al., 1996). There were no visible trends with middle ear function (e.g., notching, low resonant frequency) and the presence of hearing loss, but older individuals tended to have hearing loss greater than 20 dB HL. Many young individuals in the RA group had air-conduction thresholds poorer than normative data for the 95th percentile.

Energy Reflectance (ER) Measures

ER values, expressed as percentage, were compared between groups, using the subset of participants with TPP ± 10 daPa (28 ears in each group). A 2 x 15 (group x frequency) ANOVA with repeated measures on the second factor indicated that ER values were not significantly different between groups, $F(1, 54) = 0.038, p = 0.85$. As might be expected, an effect of frequency was found, $F(3, 171) = 155.27, p = .0001$. There was not a significant interaction between group and frequency, $F(3, 171) = .63, p = 0.61$. Pairwise comparisons revealed significant differences between most frequencies, with the exceptions being the mid-frequencies (1000-3175 Hz) and the frequencies at the high and low extremes where ER values were not significantly different. Figure 18 displays mean ER for the two groups. Figure 19 displays the mean ER and *SDs* for each group in a separate panel.

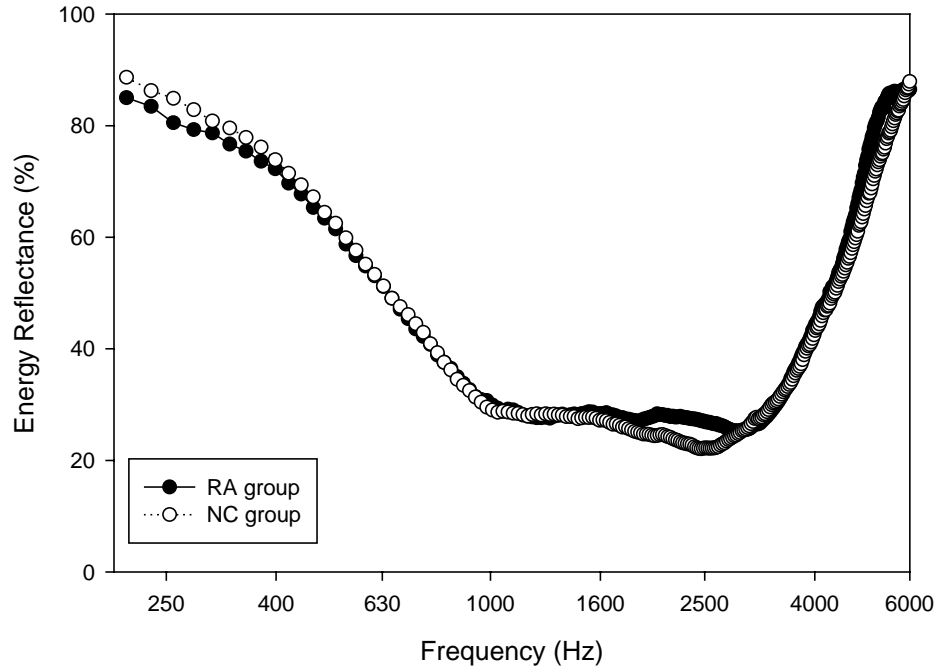


Figure 18. Mean percent of ER plotted as a function of frequency on a logarithmic scale and compared between RA (filled circles) and NC (open circles) groups (N = 28 ears per group). There were no significant differences between groups ($p > 0.05$).

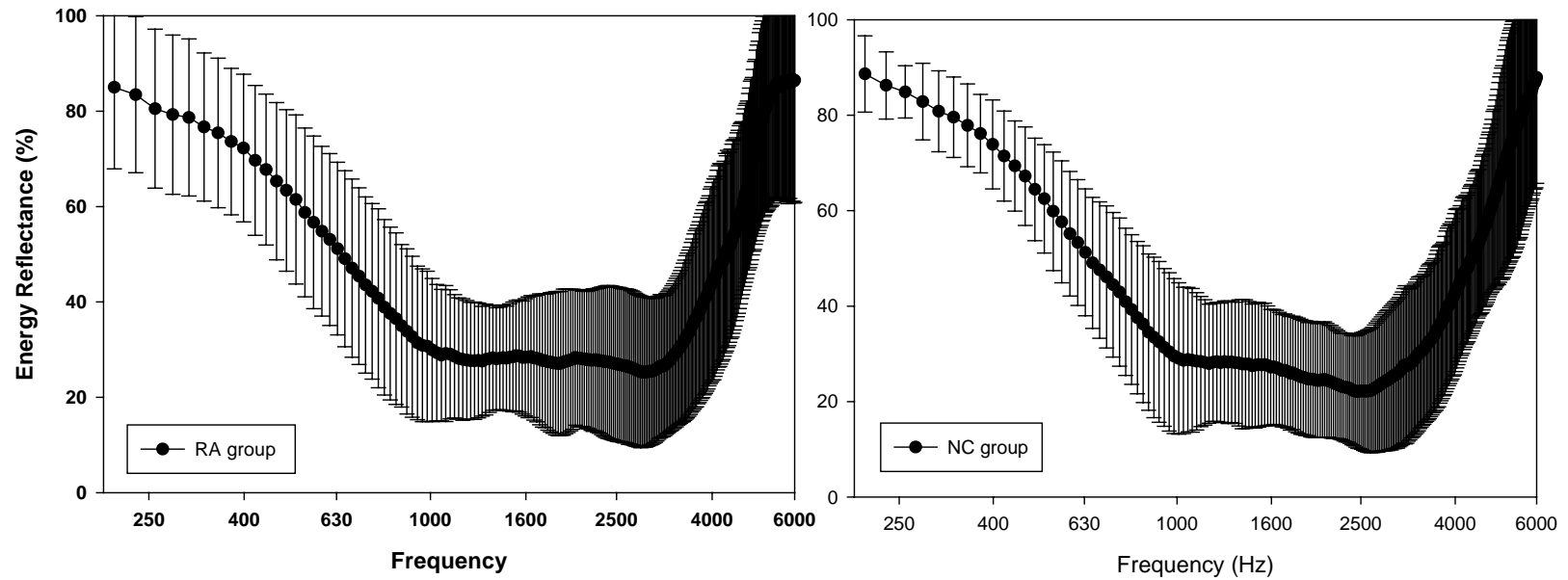


Figure 19. Mean percent of ER plotted as a function of frequency on a logarithmic scale for the RA group (left panel) and the NC group (right panel). Error bars represent $\pm SD$ from the mean. There were no significant differences between groups ($p > 0.05$).

The ER curves were further analyzed by comparing three different values obtained from the curve: (a) the frequency at which the least amount of ER occurred; (b) the value of the least amount of ER in each participant; and (c) the area under the ER curve. Values for both groups are listed in Table 11. No significant differences ($p > 0.05$) were found between groups for frequency of least ER ($t = -.12, p = 0.90$), percent of least amount of reflected energy ($t = 0.16, p = 0.87$), and area under the ER curve ($t = -.82, p = 0.42$).

DPOAE Measures

DPOAE levels were measured in the subset of 21 participants (28 ears) in each group with TPP within ± 10 daPa. Based on screening criteria (DPOAE level ≥ 10 dB SPL and DPOAE level ≥ 6 dB above the noise floor at all tested frequencies), 9/28 ears from 5 individuals in the RA group failed the screening criteria and 4/28 ears from 3 individuals in the NC group failed the screening criteria. Most of the individuals (7/8) who failed the screening were the same individuals that presented with hearing loss. One individual from the RA group did not have hearing loss, but failed the DPOAE screening bilaterally. However, this individual had the highest static admittance values between the two groups (4.8 and 2.4 mmhos), as well as middle ear resonant frequencies more than 1 *SD* below the mean for the RA group (550 and 400 Hz).

A 2 x 3 (group x frequency) ANOVA with repeated measures on the second factor indicated no significant difference in DPOAE level between groups, $F(1, 54) = 1.03, p = 0.32$. There was not a main effect of frequency, $F(2, 108) = 2.52, p = 0.09$. There was not a significant interaction between frequency and group, $F(2, 108) =$

Table 11

Comparisons of ER Measurements Between Groups

Measure	RA			NC		
	Mean	SD	Range	Mean	SD	Range
Frequency of least ER (Hz)	2165	1214	773-6000	2165	1094	820-5438
Value of least ER (%)	12.5	11.47	0.05-33.31	12.1	9.08	0.67-33.55
Area under curve	271,585	53,744	130,549- 350,335	259,944	52,798	117,275- 355,537

Note. There were no significant differences between groups ($p > 0.05$).

1.46, $p = 0.24$. Mean and standard deviations of DPOAE amplitude levels are presented in Table 12.

RA Disease Activity and Audiological Measures

The participants in the RA group had varying levels of disease involvement, as previously detailed in Table 1. Correlation analysis was performed to determine whether there was a relationship between various markers for disease involvement and either air-conduction thresholds or middle ear resonant frequency. One ear from each of the 21 participants in the RA group was selected at random for inclusion in the analysis. Measures of RA disease involvement included the level of inflammation as determined by ESR levels, number of swollen joints as determined by physicians' examination, and length of disease duration. The audiological measures were selected due to the significant differences noted between groups when comparing thresholds to age-related normative data for air-conduction thresholds, and the significantly lower resonant frequency in the RA group. Table 13 lists the Pearson's r and the level of significance for a partial correlation accounting for age and examining a relationship between RA disease factors and air-conduction thresholds and middle ear resonant frequency.

The analysis revealed a significant positive correlation between increasing disease duration and poorer air-conduction thresholds at 4000-8000 Hz. Figure 20 displays air-conduction thresholds at 4000 Hz and Figure 21 displays air-conduction thresholds at 8000 Hz as a function of disease duration. Individuals with RA who had longer disease duration had more hearing loss in the high-frequencies, even when effects of age were partialled out of the correlation analysis. However, the data appear

Table 12

DPOAE Level Comparison Between Groups

DPOAE Frequency (Hz)	RA	NC
	<i>M ± SD</i> (dB SPL)	<i>M ± SD</i> (dB SPL)
2000	2.91 ± 12.08	4.07 ± 7.64
3000	0.71 ± 14.39	3.83 ± 6.38
4000	0.32 ± 13.93	2.77 ± 8.29

Note. There were no significant differences between groups ($p > 0.05$).

Table 13

*Partial Correlations Accounting for Age and Comparing RA Disease Involvement
and Audiological Measures*

Audiologic Measure	ESR (mm/hr) <i>r</i> (<i>p</i> -level)	# Swollen Joints <i>r</i> (<i>p</i> -level)	Disease Duration (years) <i>r</i> (<i>p</i> -level)
Air-conduction:			
250 Hz	-.20 (.31)	.16 (.51)	.08 (.73)
500 Hz	-.13 (.58)	.11 (.64)	.16 (.51)
750 Hz	-.39 (.09)	-.05 (.83)	.33 (.16)
1000 Hz	-.12 (.63)	.11 (.64)	.19 (.41)
1500 Hz	-.25 (.29)	-.02 (.92)	.15 (.54)
2000 Hz	-.19 (.41)	.11 (.64)	.23 (.32)
3000 Hz	.14 (.56)	.13 (.60)	.29 (.22)
4000 Hz	.17 (.47)	-.04 (.87)	.50 (.03)*
6000 Hz	.22 (.34)	-.05 (.84)	.53 (.02)*
8000 Hz	.19 (.42)	-.06 (.81)	.53 (.02)*
Resonant Frequency (Hz)	.14 (.55)	-.33 (.12)	.04 (.87)

Note. (*) indicates significant correlations at the $p < 0.05$ level. One ear was chosen at random from each of the 21 participants for inclusion in the analysis.

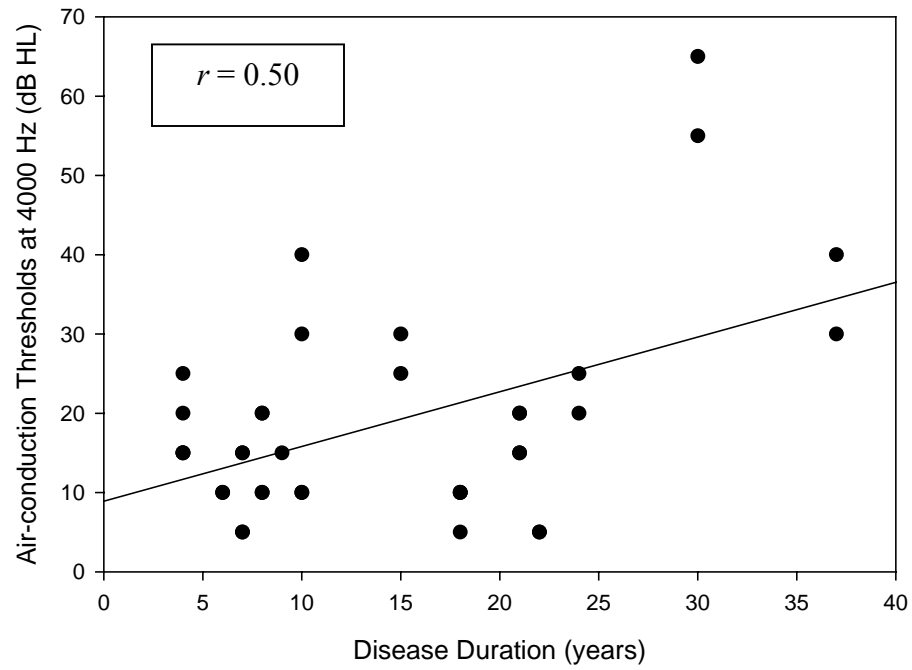


Figure 20. Scatter plot with regression line plotting the air-conduction threshold at 4000 Hz. Longer disease duration significantly correlated with a higher threshold ($p < 0.05$).

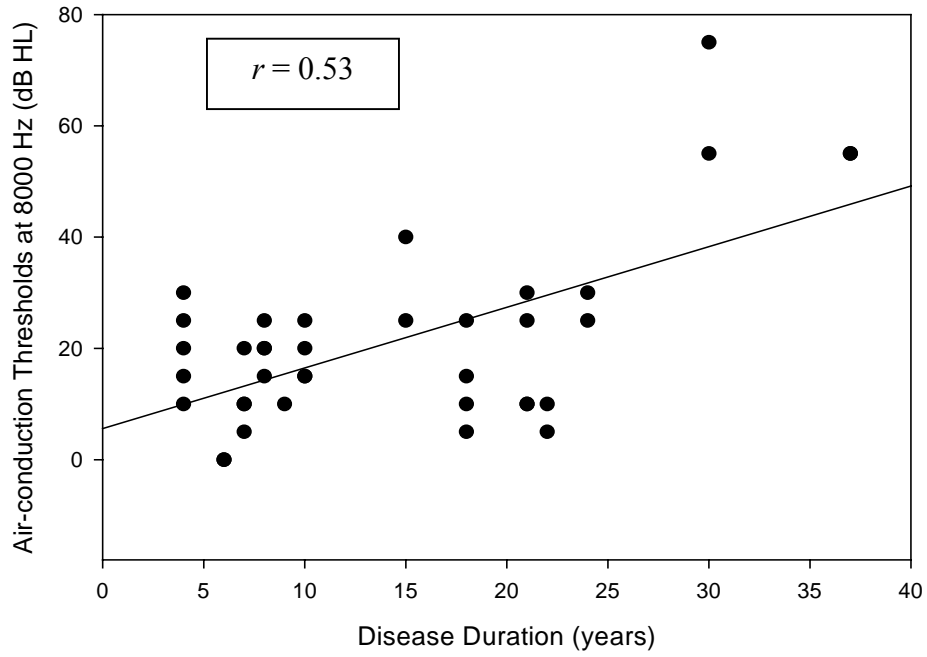


Figure 21. Scatter plot with regression line plotting the air-conduction threshold at 8000 Hz. Longer disease duration significantly correlated with a higher threshold ($p < 0.05$).

to be skewed by two older participants with long disease duration. A 59 year-old male with disease duration of 30 years, and a 61 year-old female with disease duration of 38 years both had hearing loss at 4000 Hz and 8000 Hz. When correlations were repeated without these two individuals, no significant correlations were observed. There were no correlations with air-conduction thresholds or resonant frequency and ESR levels or the number of swollen points in individuals with RA.

Although the RA group in the present study was on a variety of medication regimens, no observable trends were found regarding abnormalities in the auditory system and the medications listed in Table 1. The data were examined by comparing individuals with hearing loss, middle ear abnormalities and category of medications; however, review of the data did not display any patterns (e.g. abnormal middle ear function and use of a certain type of medication). The individuals with hearing loss and/or middle ear abnormalities were on a variety of medications.

Chapter 6: Discussion

Audiometric Measures

The purpose of this study was to determine whether individuals with RA had a greater prevalence of middle ear abnormalities and/or hearing loss compared to a group of NC participants. The groups were matched 1:1 for age and gender and carefully selected, excluding individuals from both groups based on criteria regarding middle ear history and medical history. The RA group was no more likely than the NC group to have hearing loss. This finding is inconsistent with the majority of previous studies in which a higher prevalence of hearing loss in individuals with RA than NC participants was reported (Goodwill et al., 1971 & 1972; Kastanioudakis et al., 1995; Magaro et al., 1990; Özcan et al., 2002, Raut et al., 2001; Salvinelli et al., 2004 & 2006; Takatsu et al., 2005). Participants in this study presented only with sensorineural hearing loss, which is consistent with several previous studies (Biasi et al., 1996; Goodwill et al., 1972; Kastanioudakis et al., 1995; Magaro et al., 1990). No instances of a conductive or mixed hearing loss were found, unlike other previous reports by other researchers (Raut et al., 2001; Salvinelli et al., 2004). However, sensorineural hearing loss has been the most common type of hearing loss reported in patients with RA across the literature (Kastanioudakis et al., 1995; Magaro et al., 1990).

The variance of the prevalence of hearing loss across studies may be attributed to a variety of factors, including differences in criteria used to define presence and type of hearing loss. Definitions of hearing loss have included the following: thresholds greater than 20 dB HL at two or more test frequencies (Kastanioudakis et

al., 1995; Raut et al., 2001; Takatsu et al., 2005); thresholds greater than 25 dB HL at one or more test frequencies (Halligan et al., 2006); thresholds ≥ 20 dB HL above the age-corrected level at two or more test frequencies (Öztürk et al., 2004); and greater than 20 dB below the accepted normal for the age group at two or more test frequencies (Elwany et al., 1986; Özcan et al., 2002). For those using age-corrections, the processes were not clearly explained, and this limited information about study design may also lead to inconsistencies among age-related results. Additionally, some previous studies did not clearly define any criteria for hearing loss (Djupesland et al., 1973; Goodwill et al., 1972; Reiter et al., 1980; Salvinelli et al., 2004). A clearly defined and controlled study by Halligan et al. (2006) reported that hearing loss was no more likely in individuals with RA compared to NC individuals, consistent with the current study's results.

Thresholds at 20 and 25 dB HL are considered a slight hearing loss (Clarke, 1981). The inclusion of a slight hearing loss without adjusting for age may inflate the prevalence of hearing loss, particularly in a population of individuals who tend to be older adults. For example, in the current study, seven ears from four individuals in the RA group would not have met the criteria for abnormal hearing if it was extended to greater than 25 dB HL at two or more frequencies. However, for comparison purposes the criteria of this study were varied to allow for comparison to a variety of studies.

The disparities across studies were most notable when comparing definitions of a conductive component. Raut et al. (2001) and Takatsu et al. (2005) defined a conductive component as the presence of an air-bone gap of greater than 20 dB at two

or more frequencies, and Özcan et al. (2002) used an air-bone gap greater than 5 dB as the significant criterion for a conductive component. Not surprisingly, Özcan et al. (2002) reported a higher prevalence of mixed or conductive hearing loss, 9/37 individuals with RA, compared to 6/35 and 0/36 from Raut et al. (2001) and Takatsu et al. (2005), respectively. Other studies did not clearly define criteria. Elwany et al. (1986) reported that one individual with an air-bone gap had a difference of 40 dB. These findings were in stark contrast to the prevalence of air-bone gaps reported by Salvinelli et al. (2004). The authors stated that most individuals had an air-bone gap, but did not state their criterion for a difference. Less stringent criterion may explain why 28/38 individuals with RA in their study had either a mixed or conductive type of hearing loss. The differences in criteria for a significant air-bone gap across studies make it difficult to make comparisons regarding the prevalence of different types of hearing loss in persons with RA. It appears that the prevalence of conductive and mixed hearing loss in some studies may be inflated due to questionable classification criteria, and that sensorineural hearing loss is the most prevalent finding.

The prevalence of hearing loss was not significantly different between the two groups in the current study, and there also were no significant differences between air- and bone-conduction thresholds. Other previous studies reported significant differences between air- and bone-conduction thresholds in individuals with RA compared to age- and gender-matched NC groups. Differences were most often reported in the mid-frequency range (500-2000 Hz) (Raut et al., 2001; Salvinelli et al., 2006). The current study reported a main effect of frequency for both air- and

bone-conduction thresholds. This frequency effect was expected because most participants had a high-frequency sensorineural hearing loss.

Despite the lack of difference between groups when comparing thresholds, significantly more ears from the RA group than the NC group had thresholds poorer than the 95th percentile for individuals in their age range. Most individuals in the NC group who presented with clinical hearing loss were within the expected pattern of age-related hearing loss. In the RA group, younger individuals tended to have air-conduction thresholds poorer than those expected for their age. Both males and females in the RA group presented with thresholds poorer than normative data, occurring most frequently in the mid-frequency range (1000-2000 Hz). While these thresholds were generally within clinically normal limits, these significant differences provide evidence of subtle differences in hearing sensitivity in those with RA compared to those without the disease. This finding emphasizes the need for consideration of age, and comparisons to age-appropriate normative data. Because the typical age range of individuals with RA spans the fourth to eighth decades of life, it is important to consider effects of aging when classifying hearing as normal or abnormal.

Studies that did not account for effects of aging may have overestimated the impact of RA on hearing. Several studies did not mention comparisons to normative data based on age or make adjustments accounting for effects of age (Kastanioudakis et al., 1995; Raut et al., 2001; Salvinelli et al., 2004). Given that the majority of hearing loss reported was a high-frequency sensorineural hearing loss, aging is an important factor to consider. As demonstrated in this study, even though clinical

hearing loss was typically in the high frequencies in both the RA and NC groups, no individuals in either group had a threshold poorer than the 95th percentile based on age and gender at 8000 Hz. However, other studies have factored in age-correction processes, and they still found a greater prevalence of hearing loss in the RA group compared to age- and gender-comparable NC groups (Elwany et al., 1986; Özcan et al., 2002; Öztürk et al., 2004). The results of the present study also indicated differences in the thresholds from individuals in the RA group compared to expected effects of aging, more notably in the younger participants.

Standard Immittance

Standard immittance measurements, including 226-Hz tympanometry static admittance and acoustic reflex thresholds, were not significantly different between the RA group and the NC group. Two ears from the same individual in the RA group had abnormally high static admittance (greater than 1.7 mmhos), but no ears in either group had reduced admittance (less than 0.3 mmhos), similar to the findings of Raut et al. (2001). The studies that have reported abnormal 226 tympanograms in patients with RA generally found type A_s tympanograms or reduced admittance values, which is consistent with an increase in stiffness (Elwany et al., 1986; Öztürk et al., 2004; Takatsu et al., 2005). However, some of these data may be misleading. For example, Salvinelli et al. (2004) reported individuals with active RA had reduced admittance, but their tympanograms were classified as Type A and no differences in static admittance measures were found between RA and NC groups. The static admittance values reported were still within normal limits. Similarly, studies that reported abnormal middle ear function based on tympanogram typing did not define criteria to

classify the tympanogram. Elwany et al. (1986) and Öztürk et al. (2004) reported over 50% of individuals in the RA groups had type A_s tympanograms, but the values considered abnormal are not specified.

The variability across studies may also reflect gender differences, because women have lower static admittance values than men (Margolis & Heller, 1987). Most studies used age- and gender-matched normal control groups to help reduce potential confounding factors; however, the trend of lower static admittance may reflect the higher prevalence of females involved in RA research.

Essentially, most studies conducted on RA reported no differences in acoustic reflex thresholds, consistent with the present results. One study reported prolonged acoustic reflex latency in 10% of RA participants ear (N = 45). This may be an indicator of subtle joint involvement, and further analysis of the mechanics of the acoustic reflex may be warranted.

Multi-frequency Tympanometry

The RA group had a significantly lower resonant frequency than the NC group, which suggests an increased laxity of the middle ear system or an increased effect of mass on the middle ear system. A mean resonant frequency of approximately 1000 Hz has been reported across studies using a frequency sweep method on commercially available GSI middle ear analyzers (Hanks & Rose, 1993; Margolis & Goycoolea, 1993; Valvik et al., 1994). Valvik et al. (1994) reported a 90% range for middle ear resonance of 650-1500 Hz. In the present study, 9/38 ears in the RA group and 2/38 ears in the NC group had a resonant frequency below 650 Hz. No ears in the RA group and one ear in the NC group had a resonant frequency

above 1500 Hz. The NC group had a mean of 967 Hz and was comparable with normative data. However, the RA group had a mean resonant frequency of 791 Hz, which was shifted toward the lower end of the range established by existing normative data (Valvik et al., 1994).

Other middle ear measurements conducted within individuals were usually consistent with the resonant frequency results, as demonstrated by the pattern of notched tympanograms at 678- and 1000-Hz. The prevalence of notching was not significantly different between groups; however, the RA group had more complex Vanhuysen patterns and more ears with notching, which is consistent with the resonant frequency findings. Notching was not present in the low-frequency (226 Hz) tympanometric results. A higher prevalence of notching in 660 Hz tympanograms in participants with RA has been reported by Moffat et al. (1977), Rosenberg et al. (1978), and Reiter et al. (1980).

The lower resonant frequencies and more complex tympanometric configurations suggest the admittance of the middle ear system may be mass dominated in participants with RA. Increased mass dominance is consistent with an increased laxity of the middle ear system in participants with RA. The limited research previously conducted using multi-frequency tympanometry in participants with RA reported an opposite finding, and suggested an increased stiffness in the middle ear system (Biasi et al., 1996; Colletti et al., 1997) or no difference from normal ears (Frade & Martin, 1998). Similar to the current study, these researchers did not find significant differences in audiometric thresholds between RA and NC

groups, and only observed a sensorineural hearing loss when hearing loss was present (Biasi et al., 1996; Colletti et al., 1997).

Biasi et al. (1996) and Colletti et al. (1997) found a higher resonant frequency in the RA group compared to the NC group. The test methods differed from those in the current study, in which a frequency sweep at a positive pressure (+200) using a GSI middle ear analyzer was used. In comparison, Biasi et al. (1996) and Colletti et al. (1997) determined resonant frequency by using a Virtual 310 middle ear analyzer, a negative to positive pressure sweep from -500 to +400 daPa, and frequency sweep for each air pressure value in 12.5 daPa steps. The resonant frequency was determined by the first frequency in which notching occurred in the susceptance tympanogram. The median values found by Biasi et al. (1996) and Colletti et al. (1997) were 1120 and 1250 Hz in the RA group, compared to 1000 and 1120 Hz in the matched NC group, respectively. Significant differences between groups were reported in both studies. However, individuals with RA in both studies presented with both abnormally low and high resonance, and results were not directional (Biasi et al., 1996; Colletti et al., 1997). Other researchers have reported artifact and unreliable results from using a negative to positive pressure measurement method (Holte, 1996; Shahnaz & Polka, 1997). Due to differences in measurement procedures, it is difficult to make comparisons across studies. Resonant frequency will vary based on the method and type of equipment used. The method chosen for the present study was selected because frequency sweep techniques and a positive starting pressure have been shown to provide more accurate estimates and higher test-

retest reliability than other methods (Holte, 1996; Shahnaz & Polka, 1997; Wiley, Cruickshanks, Nondahl, & Tweed, 1999).

Frade and Martin (1998) used methods and equipment identical to the present study in order to determine resonant frequency. These researchers made comparisons to existing normative data as opposed to a control group and found the mean resonant frequency in 37 individuals with RA was 998 Hz. This is higher than what was obtained by the current study, but when Frade and Martin separated the RA population into groups based on disease activity, individuals with inactive disease staging had a significantly lower resonant frequency than individuals with active disease. The lower resonant frequency obtained in the present study may also reflect the large number of individual in the RA group with low levels of inflammation and joint involvement.

The lower resonant frequency among RA participants compared to NC participants is the opposite of expected effects of age and gender on resonant frequency (Wiley et al., 1999). Wiley et al. reported no differences in resonant frequency with increasing age, but reported that older females have significantly higher resonant frequencies than older males, although the differences were small. The RA and NC groups in the current study were matched for gender, however, the sample was predominately female. Observation of a low resonant frequency in the predominantly older female RA participants as opposed to a high resonant frequency strengthens the potential argument for the influence of RA on resonant frequency.

The presence of abnormal middle ear results did not necessarily coexist with hearing loss. Some researchers concluded that the high rate of abnormal middle ear

measurements and hearing loss are related, even when the two abnormalities do not coincide (Takatsu et al., 2005). The current study did not observe any trends that abnormal middle ear findings and hearing loss coincided, similar to most existing literature (Biasi et al., 1996; Colletti et al., 1997; Öztürk et al., 2004; Raut et al., 2001; Reiter et al., 1980).

Some researchers who have reported differences in resonant frequency with no evidence of a conductive component attributed the differences to changes in the mobility of the ossicular joint (Biasi et al., 1996; Colletti et al., 1997). These researchers further suggested the stiffening of the ossicular joint could lead to long-term damage to the cochlea due to a reduction of the protective mechanism of the middle ear (Colletti et al., 1997). Moffat et al. (1977) attributed the increased laxity of the middle ear in the RA group to ligament anchorage of the ossicles. Reiter et al. (1980) hypothesized that the changes to the ossicular joints affected the normal leverage function of the middle ear joints, increasing the mass of the system, and thus lowering the resonant frequency. While these theories are reasonable based on what is known about how RA affects other synovial joints in the body, it is difficult to draw firm conclusions. It can be hypothesized that subtle effects of the disease increase the mass dominance of the middle ear by effecting the leverage action of the middle ear joints. The fact that a lower resonant frequency did not correlate with the number of swollen joints or ESR levels in the current study provides no additional support to this claim. This hypothesis would need to be corroborated with examination of the middle ear joints, which is not practical in living humans. Additional temporal bone studies would help to clarify the effects of RA on middle

ear structures and potential reasons for abnormal middle ear findings. The present study did not observe trends of lower resonant frequency corresponding with hearing loss. Because other studies failed to correlate middle ear abnormalities and hearing loss, it seems the differences in middle ear sound transmission may not affect hearing sensitivity.

While cases of middle ear abnormalities correlating with conductive hearing loss have been reported in cases of RA, these seem to be more rare instances. Subtle but significant differences in the mass components of the middle ear systems in the RA group compared to the NC group would not necessarily be expected to cause hearing loss. While some researchers have gone a step further to suggest that changes to the middle ear system resulting from RA may affect the protective mechanism of the middle ear, this theory does not seem reasonable, particularly because most of the hearing loss noted in the current study was within the age expected range. Acoustic reflex thresholds more directly assess the protective functioning of the middle ear system, and should theoretically provide more information about any changes in this mechanism. Normal acoustic reflex thresholds in RA participants are one of the few consistent findings reported across the literature. Future studies examining the latency and amplitude of middle ear reflexes may provide further information.

ER and DPOAE Measures

Although differences in resonance frequency were observed between groups, differences in ER measurements between groups were not found. ER measurements were very similar between groups, even though the RA group had a significantly lower resonant frequency. This may be due to the large range of normative values for

ER, making subtle differences that do not cause conductive components difficult to identify. Another factor might be that differences between individuals are averaged out in the analysis process. Keefe et al. (1993) and Feeney and Sanford (2004) acknowledged concerns that averaged data reduced the depth of the point of least ER, because the deepest ER point occurred at various frequencies. However, the current study compared the frequency at which the least amount of ER occurred, as well as the lowest amount of energy reflected, and still found no significant differences. The discrepancy that significantly lower middle ear resonant frequencies were recorded in the RA group compared to the NC group, but that no differences were found comparing ER between groups, cannot easily be explained. It would be expected that if there were a difference in the laxity or mass dominance of the middle ear system, as middle ear resonant frequency results suggest, it should also be reflected in ER data. Some individual results varied from the mean ER; however, this was true for ears in the NC group, as well. These variances generally consisted of shifts in the peak of lowest frequency, and the variance observed in the included ears did not visually differ as much as excluded ears (e.g., negative middle ear pressure as displayed previously in Figure 7). Figure 22 displays the average ER values obtained in this study compared to existing normative data.

Average ER values measured in RA and NC groups in the present study were lower across frequencies from 250 – 2000 Hz and higher for frequency above 4000 Hz compared to other normative data. This difference is consistent for both groups. The differences may be due to equipment differences. Shahnaz and Bork (2006) were the only study conducted using the commercially available Mimosa reflectance

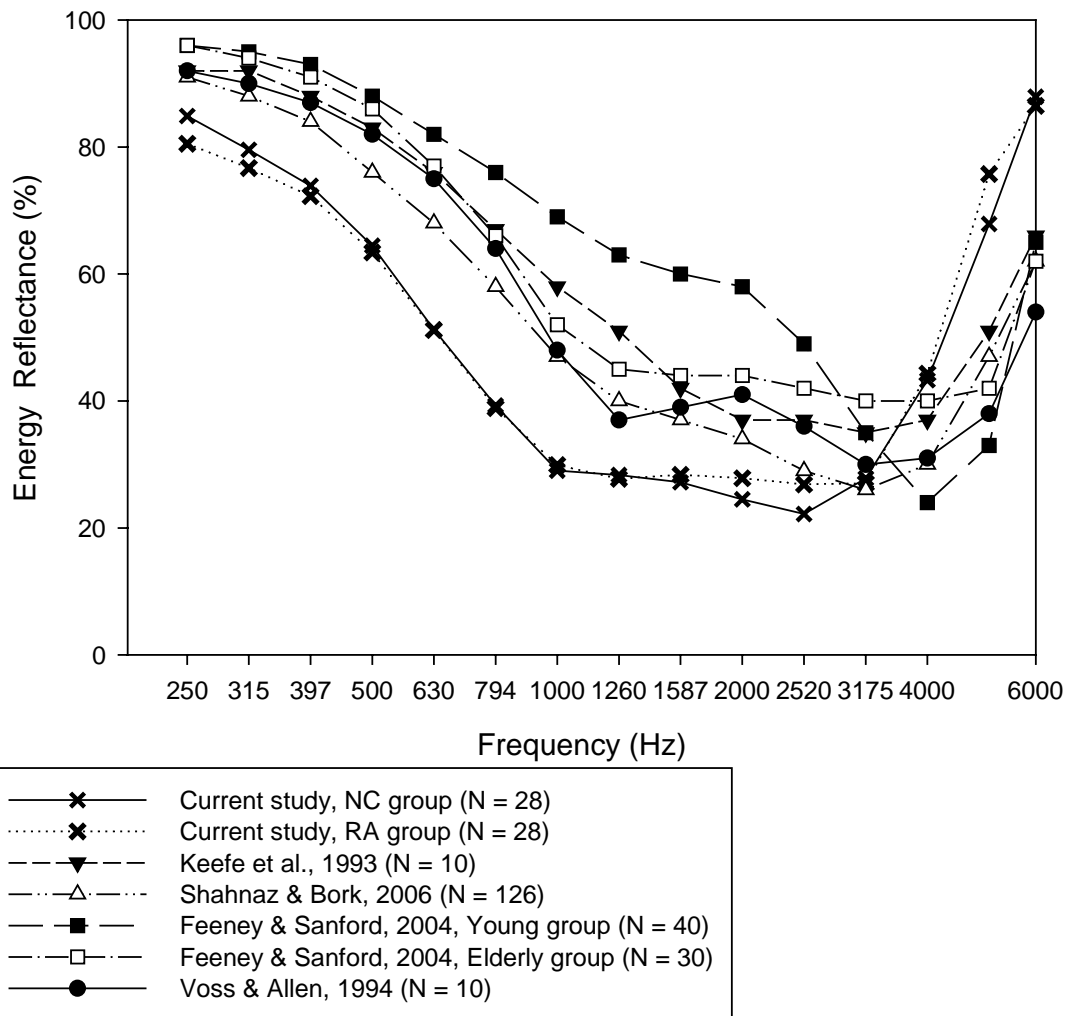


Figure 22. Comparison of group mean ER values as a function of frequency across different studies. ER values used for Keefe et al. (1993) and Voss and Allen, (1994) were obtained from printed values in Shahnaz and Bork (2006).

system and their data most closely resemble those from this study. Figure 23 compares mean ER data obtained in the current study to the 95th percentile range obtained by Shahnaz and Bork (2006). Although the mean ER slightly differed compared to other studies as shown in Figure 22, the curve was within the 95% range based on data obtained from 126 ears using the Mimosa system as shown in Figure 23 (Shahnaz & Bork, 2006). However, the ER values in the present study, especially at the low frequencies, are very close to the edge of this range. Differences may also be attributed to method. Shahnaz and Bork (2006) used one test run for analysis, compared to the present study, which found the mean of three test runs. Although the deviation from different test runs in the current study was small, these efforts helped to ensure test-retest reliability within each individual and may explain some, albeit most likely small, differences when comparing studies.

Another factor that likely contributed to the ER differences seen in the present study is age. Feeney and Sanford (2004) also demonstrated a significant decrease in ER from 794 – 2000 Hz, and significantly higher ER at 4000 Hz in their sample of older adults. The normative data obtained by Shahnaz and Bork (2006) included 126 adults (237 ears) although inclusion criteria did not specify a requirement for TPP, and the individuals included were younger adults (20 – 32 years) than those in the current study. The current study carefully controlled for TPP and included older adults, which may contribute to the difference in ER between studies. Despite the observable differences compared to normative data, the general shape is consistent across studies, unlike in pathological ears (Feeney et al., 2003).

No difference in DPOAE levels at 2000, 3000, and 4000 Hz were noted

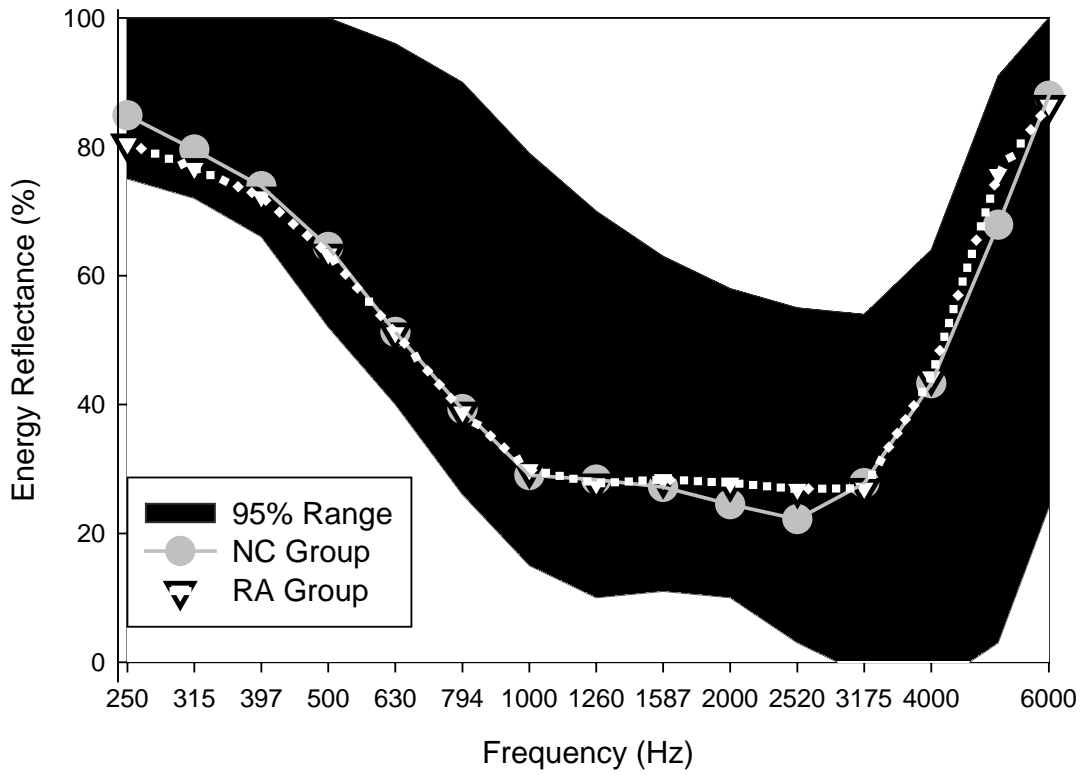


Figure 23. Group comparison of mean ER curves obtained for the RA and NC groups in the current study, compared to the 95% range for normative data from Shahnaz and Bork (2006).

between the RA and NC groups. Halligan et al. (2006) also reported no significant differences between groups in TEOAEs at 1000, 1500, 2000, 3000, and 4000 Hz. In contrast, Salvinelli et al. (2006) reported a significant difference in TEOAE reproducibility and level between RA and NC groups; however, their otologic screening criteria were not as stringent as in this and other studies. The DPOAE results in the present study were consistent with expected outcomes based on audiometric results obtained within individuals. The individuals that failed the DPOAE screening in the present study had hearing loss and middle ear abnormalities (hypermobile tympanic membrane).

RA Demographics

Only limited information is available regarding the effects of rheumatic medications, but no known ototoxic effects have been reported (Kastanioudakis et al., 1995). Halligan et al. (2006) observed hearing loss in an increased number of RA participants who were taking hydroxychloroquine, a type of DMARD; however, in the current study, only two of the eight individuals with hearing loss in the RA group were taking this medication, compared to 7/21 from the overall group taking this medication. Although the RA participants in the present study were on a variety of medication regimens, no observable trends were found regarding abnormalities in the auditory system and medication. This is consistent with the findings of other researchers who did not find correlations between medications used to manage RA and hearing loss (e.g., Kastanioudakis et al., 1995; Takatsu et al., 2005).

Mixed results have been reported about the level of involvement of RA disease activity and hearing loss. In the present study, longer disease duration

correlated with poorer air-conduction thresholds at 4000-8000 Hz. Individuals with long disease duration would typically be older participants, and would be expected to have more hearing loss as an effect of age. Therefore, it was necessary to partial out age in the analysis, and a significant relationship was still found. However, due to the small sample size in this study, two older individuals with hearing loss and longstanding disease duration may have potentially skewed the correlation data. When correlations were repeated without these two individuals, no significant correlations were observed. However, these individuals had hearing thresholds poorer than expected based on their age and their exclusion was not warranted. Because the sample size in the current study is small, individuals such as these may have a greater impact on overall results than in larger sample sizes and this correlation should be viewed cautiously. In contrast, other studies did not find a correlation with disease duration and hearing loss (e.g., Takatsu et al, 2005). Future studies might examine the hearing in children with juvenile RA, which may enable researchers to differentiate effects of age and the effects of RA on audiological measures. Giannini et al. (1997) found children with juvenile RA had significantly higher mean resonant frequency than a control group of children. Audiometric measures were not obtained in their study, but their results helped to suggest an effect of RA on middle ear resonant frequency independent of age.

Other factors to consider are the variability in disease involvement with RA. RA can affect different joints in different individuals, and can have varying levels of involvement and inflammation within the same individual. Factors such as disease duration and disease activity are not clearly discussed in many studies, which makes

comparisons difficult across the literature (Kakani et al., 1990; Öztürk et al., 2004; Raut et al., 2001). Based on the results presented in the current study in Table 1, most of the individuals with RA had low levels of disease involvement reflected by a lack of swollen joints, and inflammation levels that were not significant. This may have contributed to the lack of hearing loss found in this study compared to the NC group.

Only a few studies have reported significant correlations between markers of disease involvement and hearing loss. Takatsu et al. (2005) reported individuals with RA and sensorineural hearing loss had higher ESR levels than individuals without hearing loss. Goodwill et al. (1972) reported individuals with RA that had nodules had significantly poorer hearing than those without nodules. Frade et al. (1998) reported individuals with active disease staging had higher resonant frequencies than individuals with inactive disease staging. Additionally, a case report by Nores and Bonfils (1988) showed a decrease in hearing in a person with RA associated with a flare-up, and improvement five months later following medical management of the disease through corticosteroids. However, others have reported no correlations between hearing measures and medications, disease duration, or disease stage (Giannini et al., 1997; Halligan et al., 2006; Salvinelli et al., 2004).

The present study found a correlation with increased disease duration and poorer audiometric thresholds. These significant correlations should be viewed cautiously due to the small sample size, and that the data could be heavily influenced by trends of a few as opposed to trends of the group. Further research with a larger sample of patients with RA would be helpful to substantiate this relationship.

Chapter 7: Conclusions

The nature and type of hearing loss in individuals with RA has been widely debated, and existing research has varied. The potential causes of hearing loss in individuals with RA have been attributed to effects on the middle ear joints from the RA disease process, vasculitis or neuritis, or ototoxic medication. While there has been consensus about potential causes of hearing loss, the reported extent and influence of RA on the middle and/or inner ear have been varied.

Results from the current study revealed the RA group was no more likely to have hearing loss than the NC group. There were no differences in air- and bone-conduction thresholds between groups. Audiometric results revealed only sensorineural hearing loss in both groups; no individuals presented with a conductive component. The RA group, however, had a significantly greater number of thresholds poorer than the 95th percentile based on age and gender. In particular, a large number of young participants with RA had thresholds worse than expected for their age. These significant differences highlight the importance of considering age effects for both abnormal and normal hearing thresholds. The individuals in the NC group with clinical hearing loss had thresholds that fell within the expected range for their age. In comparison, younger RA participants had normal clinical hearing sensitivity, but their thresholds were poorer than the 95th percentile in their age group, occurring most frequently in the mid-frequency range (1000-2000 Hz).

Resonant frequency was significantly lower for the RA group versus the NC group. However, no other significant differences were found for other middle ear measures (226-Hz static admittance, multi-frequency tympanometric configurations,

and multi-frequency static admittance). The presence of notching at 678- and 1000-Hz tympanograms was not significantly different between groups, but the RA group had more complex notching patterns, which is consistent with resonant frequency findings. Although a statistically significant difference was found with regard to resonant frequency, the difference between groups was slight. The lower resonant frequency is consistent with an increased laxity or mass dominance of the middle ear system. However, because this was the only abnormal middle ear finding, it is difficult to draw strong conclusions.

The differences in middle ear sound transmission implied by a lower mean resonance frequency in the RA group were not corroborated by ER measures. No differences in ER measurements were found between the RA and NC group. There is a broad range of normative data for ER, and limited research has been conducted to date. Additional research is needed with larger samples to provide information about ER changes in ears with middle ear disorders. In addition, no differences in DPOAE levels were found between the RA and NC group.

Longer RA disease duration correlated with high-frequency air-conduction thresholds. Due to the small sample size, these significant findings may have been skewed by a few select individuals and should be viewed cautiously. The presence of abnormal middle ear measurements and hearing loss did not coincide in the current study. This suggests that subtle middle ear differences in this population do not necessarily manifest as hearing loss. This may explain why audiological considerations are often overlooked in the RA population. The differences may be subtle and have limited clinical significance. It appears conductive involvement is

possible from previous studies, but may be rare. It is difficult to draw strong conclusions about the underlying mechanism of change in the auditory system in individuals with RA.

Currently, only pilot or preliminary studies have been conducted examining the effects of the disease process within individuals over time. The majority of research on RA and hearing loss and middle ear function has utilized a cross-sectional design, and therefore, longitudinal studies would help to provide additional clarification. Testing individuals when they first present with symptoms would help to provide results before and after treatment and about potential ototoxic effects of the medications often prescribed in this population. Additional studies examining a greater number of individuals with active RA would provide information about the correlation between RA and audiological manifestations. Longitudinal studies in individuals with active RA could help reveal whether effects are transitory or permanent, and, associated with flares in disease involvement. Additional studies are needed to examine younger adults with RA and an earlier onset of hearing loss than in the normal population. The significant findings in this study show the importance of monitoring individuals with RA for potential audiological manifestations, and suggest the possible inclusion of an audiological evaluation in the test battery for individuals with RA.

Appendix A

Consent Form

Initials _____ Date _____

CONSENT FORM

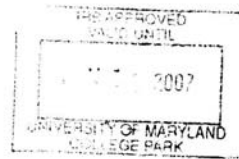
Page 1 of 3

Project Title	<i>Wideband Reflectance in Adults with Rheumatoid Arthritis</i>
Why is this research being done?	<i>This is a research project being conducted by Caroline Roberts (student investigator) and Dr. Tracy Fitzgerald (primary investigator) at the University of Maryland, College Park in collaboration with Dr. Carmen Brewer (co-investigator) at the National Institutes of Health. We are inviting you to participate in this research project because you are at least 18 years of age and you are currently diagnosed with rheumatoid arthritis, or are at least 18 years old with no known arthritic diseases. The purpose of this research project is to measure the effects of rheumatoid arthritis on middle ear function.</i>
What will I be asked to do?	<p><i>The procedures will be conducted within one session of approximately one hour.</i></p> <p><i>You will be asked to complete a questionnaire on general health and ear health.</i></p> <p><i>A small hand-held scope much like a flashlight with a plastic tip will be placed in the opening of the ear so that the investigator can inspect the ear canal.</i></p> <p><i>You will undergo a hearing test. During this test you will be asked to listen to tones and indicate that you hear them by raising your hand, pressing a button, or responding verbally. The tones will be presented through earphones and then through a small vibrator placed behind your ear. You will be asked to repeat back words heard through earphones.</i></p> <p><i>You will undergo several tests to assess function of the middle and inner ear. No response will be required during these tests, but you will be asked to sit quietly. First, plugs covered with soft rubber tips will be placed in the opening of your ears. You will hear a buzzing tone coming from the plug and feel a slight pressure change. Next, you will hear some short loud tones coming from the plug. Finally, a different plug with a soft foam tip will be placed in the opening of your ear. You will hear a variety of chirps and tones coming from the plug. The results of the hearing test will be explained to you.</i></p> <p><i>All testing will take place either in the Clinical Center, Building 10 on the fifth floor at the National Institute on Deafness and Other Communication Disorders (NIDCD), National Institutes of Health (NIH) in Bethesda, Maryland, or in the Hearing Clinic and Dr. Fitzgerald's Laboratory located in Lefrak Hall on the University of Maryland, College Park campus.</i></p>

Project Title	<i>Wideband Reflectance in Adults with Rheumatoid Arthritis</i>
What about confidentiality?	<p><i>We will do our best to keep your personal information confidential. To help protect your confidentiality your name will not be included on collected data and a code will be used on the collected data. The investigators will be able to link your survey to your identity through the use of an identification key; however, only the investigators will have access to the identification key. If we write a report or article about this research project, your identity will be protected to the maximum extent possible.</i></p> <p><i>Your information may be shared with representatives of the University of Maryland, College Park or governmental authorities if you or someone else is in danger or if we are required to do so by law.</i></p>
What are the risks of this research?	<p><i>There are some risks from participating in this research study. Several sounds, including tones, clicks, and noise, will be presented to your ears. The sounds will not be presented at durations that could cause damage to the auditory system; however, the sounds may be uncomfortable or unpleasant to you. Please notify the investigators immediately if you experience any discomfort.</i></p>
What are the benefits of this research?	<p><i>This research is not designed to help you personally, but the results may help the investigator learn more about the effects of rheumatoid arthritis on middle ear function. We hope that, in the future, other people might benefit from this study through improved understanding of the effects of rheumatoid arthritis on the middle ear.</i></p>
Do I have to be in this research? May I stop participating at any time?	<p><i>Your participation in this research is completely voluntary. You may choose not to take part at all. If you decide to participate in this research, you may stop participating at any time. If you decide not to participate in this study or if you stop participating at any time, you will not be penalized or lose any benefits to which you otherwise qualify.</i></p>
Is any medical treatment available if I am injured?	<p><i>The University of Maryland does not provide any medical, hospitalization or other insurance for participants in this research study, nor will the University of Maryland provide any medical treatment or compensation for any injury sustained as a result of participation in this research study, except as required by law.</i></p>

Project Title	Wideband Reflectance in Adults with Rheumatoid Arthritis	
What if I have questions?	<p><i>This research is being conducted by Tracy Fitzgerald at the University of Maryland, College Park. If you have any questions about the research study itself, please contact Tracy Fitzgerald at:</i></p> <p>Department of Hearing and Speech Sciences University of Maryland, College Park College Park, MD 20742 301-405-4224 tfitzgerald@hesp.umd.edu.</p> <p><i>If you have questions about your rights as a research subject or wish to report a research-related injury, please contact: Institutional Review Board Office, University of Maryland, College Park, Maryland, 20742; (e-mail) irb@deans.umd.edu; (telephone) 301-405-0678</i></p> <p><i>This research has been reviewed according to the University of Maryland, College Park IRB procedures for research involving human subjects.</i></p>	
Statement of Age of Subject and Consent	<p><i>Your signature indicates that:</i></p> <p><i>you are at least 18 years of age;</i></p> <p><i>the research has been explained to you;</i></p> <p><i>your questions have been fully answered; and</i></p> <p><i>you freely and voluntarily choose to participate in this research project.</i></p>	
Signature and Date	NAME OF PARTICIPANT (Please print)	
	SIGNATURE OF PARTICIPANT	
	DATE	

If you would be interested in participating in future studies, please provide us with your contact information (phone and/or email):



Appendix B

General Health Questionnaire

Participant Number: _____ Date: _____

Age: _____ Sex: (circle) Male Female

Race: (circle)

African American Asian Caucasian Hispanic Pacific Islander
 Native American Other _____

Responses may be reviewed orally for any necessary clarification.

Please check the appropriate response (yes or no) to each question:

	Yes	No
1. Have you been clinically diagnosed with rheumatoid arthritis (RA) by a physician? <i>If you answer "Yes," please skip questions #2-10.</i>		
2. Do you experience morning stiffness in and around the joints, lasting at least 1 hour?		
3. Do you have tender, warm, swollen joints?		
4. Do you have joint inflammation affecting the wrists, hands or fingers?		
5. Do you have simultaneous involvement/inflammation of the same joint area on both sides of the body? Symmetrical arthritis?		
6. Do you have rheumatoid nodules?		
7. Have you tested positive for a serum rheumatoid factor?		
8. Do you experience joint pain or stiffness?		
9. Have you had radiographic images that show erosions or bony decalcification of the hands or wrist?		
10. Has anyone in your family been diagnosed with rheumatoid arthritis or rheumatism?		

	Yes	No
11. Have you previously been diagnosed with hearing loss?		
12. Do you have a history of ear infections?		
13. Have you had any medical problems involving your ears?		
14. Have you had any surgeries involving your ears, nose or throat?		
15. Have you had an upper respiratory infection within 30 days?		
16. Do you have sinus problems?		
17. Do you have a history of noise exposure (e.g. military service, occupational noise)?		
18. Do you have ringing or sounds in your ears (tinnitus)?		
19. Do you experience problems with dizziness or balance?		
20. Do other members of your family have hearing loss?		

	Yes	No
21. Have you sustained any type of head injury or trauma?		
22. Do you have any head or neck abnormalities that have been present since birth?		
23. Have you been diagnosed with any neurologic disease?		
24. Have you ever been diagnosed or treated for cancer?		
25. Have you ever been diagnosed with any other serious illness(es)?		

Please list all current medications:

Please list any other significant medical surgeries or illnesses:

References

- Allen, J. B. (1985). Measurement of eardrum acoustic impedance. In J. B. Allen, J. L. Hall, A. Hubbard, S. T. Neely, and A. Tubis (Eds.) *Peripheral Auditory Mechanisms*, (pp.44-51). Berlin: Springer-Verlag.
- Allen, J. B., Jeng, P. S., & Levitt, H. (2005). Evaluation of human middle ear function via an acoustic power assessment. *Journal of Rehabilitation Research & Development*, 42, 63-78.
- American National Standards Institute. (2004). *Specification for audiometers*. (ANSI S3.6-2004). New York: Author.
- American National Standards Institute. (2002). *Specifications for instruments to measure aural acoustic impedance and admittance (aural acoustic immittance)*. (ANSI S3.39-2002). New York: Author.
- Arnett, F. C., Edworthy, S. M., Bloch, D. A., McShane, D. J., Fries, J. F., Cooper, N. S., Healey, L. A., Kaplan, S. R., Liang, M. H., Luthra, H. S., Medsger, Jr., T. A., Mitchell, D. M., Neustadt, D. H., Pinals, R. S., Schaller, J. G., Sharp, J. T., Wilder, R. L., & Hunder, G. G. (1988). The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis and Rheumatism*, 31, 315-324
- Biasi, D., Fiorino, F., Carletto, A., Caramaschi, P., Zeminian, & Bambara, L. M. (1996). Middle ear function in rheumatoid arthritis: a multiple frequency tympanometric study. *Clinical and Experimental Rheumatology*, 14, 243-247.

- Brazeau-Lamontagne, L., Charlin, B., Levesque, R., & Lussier, A. (1986).
Cricoarytenoiditis: CT assessment in rheumatoid arthritis. *Radiology*, *158*,
463-466.
- Calandruccio, L., Fitzgerald, T. S., & Prieve, B. A. (2006). Normative multifrequency
tympanometry in infants and toddlers. *Journal of the American Academy of
Audiology*, *17*, 470-480.
- Camilleri, A. E. (1991). Nature of the ossicular joints and their involvement in
rheumatoid arthritis. *Annals of the Rheumatic Diseases* *50*, 271.
- Clarke, J. G. (1981). Uses and abuses of hearing loss classification. *ASHA*, *23*, 493-
500.
- Colletti, V. (1976). Tympanometry from 200 to 2000 Hz probe tone. *Audiology*, *15*,
106-119.
- Colletti, V., Fiorino, F. G., Bruni, L., & Biasi, D. (1997). Middle ear mechanics in
subjects with rheumatoid arthritis. *Audiology*, *36*, 136-146.
- Copeman, W. S. (1963). Rheumatoid oto-arthritis. *British Medical Journal*, *5371*,
1526-1527.
- Cush, J. J., Kavanaugh, A., & Stein, C. M. (Eds.) (2005). *Rheumatology: Diagnosis
and Therapeutics*. (2nd Ed.). Philadelphia: Lippincott Williams & Wilkins.
- Djupesland, G., Grønås, H. E., & Saxegaard, E. F. (1973). Hearing and middle-ear
function in patients with inflammatory rheumatoid joint diseases.
Scandinavian Journal of Rheumatology, *2*, 53-56.
- Elwany, S., Garf, A. E., & Kamel, T. (1986). Hearing and middle ear function in
rheumatoid arthritis. *The Journal of Rheumatology*, *13*, 878-881.

- Feeney, P. (2005, April 12). Wideband energy reflectance. *The ASHA Leader*, pp. 6-7, 24.
- Feeney, M. P., Grant, I. L., & Marryott, L. P. (2003). Wideband energy reflectance measurements in adults with middle-ear disorders. *Journal of Speech, Language, and Hearing Research*, 46, 901-011.
- Feeney, M. P. & Sanford, C. A. (2003). The aging middle ear: wideband energy reflectance measurement. *Journal of the Acoustical Society of America*, 113, 2226.
- Feeney, M. P., & Sanford, C. A. (2004). Age effects in the human middle ear: wideband acoustical measures. *Journal of the Acoustical Society of America*, 116, 3546-3558.
- Fowler, C. G., & Shanks, J. E. (2002). Tympanometry. In J. Katz (ed.) *Handbook of Clinical Audiology*, 5th ed. Philadelphia: Lippincott Williams & Wilkins.
- Frade, C., & Martin, C. (1998). Diagnostic value of the multifrequency tympanometry in active rheumatoid arthritis. *Auris, Nasus, Larynx*, 25, 131-136.
- Gairola, A., Kacker, S., Kumar, A., & Malaviya, A. (1991). Laryngeal and ear involvement in rheumatoid arthritis in north India. *British Journal of Rheumatology*, 30, 65-66.
- Giannini, P., Marciano, E., Strano, C. G., Alessio, M., Marcelli, V., & Auletta, G. (1997). Middle ear involvement in children with chronic rheumatoid juvenile arthritis. *European Archives of Otorhinolaryngology*, 254(Suppl. 1), S30-S33.

- Goodwill, C. J., Lord, I. J., & Knill-Jones, R. P. (1971). Hearing in rheumatoid arthritis: Results of audiometry in 76 patients. *Annals of the Rheumatic Diseases, 30*, 329-331.
- Goodwill, C. J., Lord, I. J., & Knill-Jones, R. P. (1972). Hearing in rheumatoid arthritis: A clinical and audiometric survey. *Annals of the Rheumatic Diseases, 31*, 170-173.
- Greenhouse, S. W., & Geisser, S. (1959). On methods in the analysis of profile data. *Psychometrika, 24*, 95–112.
- Gussen, R. (1971). The human incudomalleal joint: Chondroid articular cartilage and degenerative arthritis. *Arthritis and Rheumatism, 14*, 465-474.
- Gussen, R. (1977). Atypical ossicle joint lesions in rheumatoid arthritis with sicca syndrome (Sjögren syndrome). *Archives of Otolaryngology, 103*, 284-286.
- Haberkamp, T J., & Tanyeri, H. M. (1999). Management of sudden sensorineural hearing loss. *American Journal of Otolaryngology, 20*, 587-595.
- Halla, J. T., & Hardin, J. G. (1988). Salicylate ototoxicity in patients with rheumatoid arthritis: a controlled study. *Annals of the Rheumatic Diseases, 47*, 134-137.
- Halligan, C.S., Bauch, C. D., Brey, R. H., Achenbach, S. J., Bamlet, W. R., McDonald, T. J., & Matteson, E. L. (2006). Hearing loss in rheumatoid arthritis. *The Laryngoscope, 116*, 2044-2049.
- Hanks, W. D. & Mortensen, B. A. (1997). Multifrequency tympanometry: effects of ear canal volume compensation on middle ear resonance. *Journal of the American Academy of Audiology, 8*, 53-58.

- Hanks, W.D. & Rose, K.J. (1993). Middle ear resonance and acoustic immittance measures in children. *Journal of Speech and Hearing Research*, 36, 218-222.
- Harris, E. D. Jr. (2005). Clinical Features of Rheumatoid Arthritis. In E. D. Harris Jr., R. C. Budd, M. C. Genovese, G. S. Firestein, J. S. Sargent, C. b. Sledge & S. Ruddy (Eds.) *Kelley's textbook of Rheumatology, Seventh Edition, vol. 2*. (pp1043-1066). Philadelphia: Elsevier Saunders.
- Heyworth, T., & Liyanage, S. P. (1972). A pilot survey of hearing loss in patients with rheumatoid arthritis. *Scandinavian Journal of Rheumatology*, 1, 81-83.
- Hinchcliffe, R. (1958). The pattern of the threshold of perception for hearing and other special senses as a function of age. *Gerontologia*, 2, 311-320.
- Hocke, T., Eiber, A., Vorwerk, U., Pethe, J., Muhler, R., von Specht, H. & Begall, K. (2000). Resonant frequency pattern in multifrequency tympanograms: results in normally-hearing subjects. *Audiology*, 39, 119-24.
- Holte, L. (1996). Aging effects in multifrequency tympanometry. *Ear and Hearing*, 17, 12-18.
- Holte, L. & Margolis, R. H. (2002). Contemporary research in tympanometry. *Current Opinion in Otolaryngology & Head and Neck Surgery*, 10, 387-391.
- Hunder, G. G. (Ed.). (1999). *Mayo clinic on arthritis*, New York: Kensington Publishing Company.
- Hunter, L. L. (2004, March). Wideband reflectance in infants and children with middle ear effusion [abstract]. 2004 American Auditory Society Science and Technology Meeting, Scottsdale, AZ.

- Hunter, L.L. and Margolis, R.H. (1992). Multifrequency tympanometry: Current clinical application. *American Journal of Audiology*, 1, 33-43.
- Hüttenbrink, K. B. (1998). Die mechanik der Gehörknöchelchen bei statischen Drucken. [Ossicle chain mechanics at static air pressure II: impaired joint function and reconstructed ossicles chain (Abstract).] *Laryngology, Rhinology, and Otolology*, 67, 100-105.
- ISO (1984). Acoustics – Threshold of hearing by air conduction as a function of age and sex for otologically normal persons. (Ref. No. 7029-1984), 1-8.
- Jeng, P. S., Levitt, H., Lee, W.W., & Gravel, J.S. (2001, June). Reflectance Measurements for Detecting OME in Children: Preliminary Findings. Proceedings of the Seventh International Symposium: Recent Advances in Otitis Media with Effusion, Ft. Lauderdale, FL.
- Jerger, J. (1970). Clinical experience with impedance audiometry. *Archives of Otolaryngology*, 92, 311–324.
- Jerger, J. & Jerger, S. (1974). Studies in impedance audiometry. *Archives of Otolaryngology*, 99, 165-171.
- Kakani, R.S., Mehra, Y. N., & Mehta, S. (1990). Audiovestibular functions in rheumatoid arthritis. *Journal of Otolaryngology*, 19, 100-102.
- Kastanioudakis, I., Skevas, A., Danielidis, B., Tsiakou, E., Drosos, A., & Moustopoulos, M. H. (1995). Inner ear involvement in rheumatoid arthritis: a prospective clinical study. *The Journal of Laryngology and Otolology*, 109, 713-718.

- Keefe, D. H., Bulen, J. C., Arehart, K. H., & Burns, E. M. (1993). Ear-canal impedance and reflection coefficient in human infants and adults. *Journal of the Acoustical Society of America*, *94*, 2617-2638.
- Keefe, D. H., Ling, R., & Bulen, J. C. (1992). Method to measure acoustic impedance and reflection coefficient. *The Journal of the Acoustical Society of America*, *91*, 470-485.
- Keefe, D. H., & Simmons, J. L. (2003). Energy transmittance predicts conductive hearing loss in older children and adults. *Journal of the Acoustical Society of America*, *114*, 3217-3238.
- Kolman, J., & Morris, I. (2002). Cricoarytenoid arthritis: a cause of acute upper airway obstruction in rheumatoid arthritis. *Canadian Journal of Anesthesia*, *49*, 729-732.
- Kovarsky, J. (1984). Otorhinolaryngologic complications of rheumatic diseases. *Seminars in Arthritis and Rheumatism*, *14*, 141-150.
- Liden, G. (1969). The scope and application of current audiometric tests. *Journal of Laryngology and Otology*, *83*, 507-520.
- Liening, D. A., & Larouere, M. J. (1997). Relief of sensorineural hearing loss due to rheumatoid arthritis by endolymphatic sac decompression. *The Journal of Otolaryngology*, *26*, 281-283.
- Lilly, D. (2005). The evolution of aural acoustic-immittance measurements. *The ASHA Leader*, pp. 6, 24.
- Lipscomb, D. L. (1996). The external and middle ear. In J. L. Northern, *Hearing Disorders*, 3rd Ed., Boston: Allyn and Bacon.

- Magaro, M., Zoli, A., Altomonte, L., Mirone, L., Corvino, G., DiGirolamo, S., Giacomini, P., & Alessandrini, M. (1990). Sensorineural hearing loss in rheumatoid arthritis. *Clinical and Experimental Rheumatology*, 8, 487-490.
- Maini, R. N., & Feldmann, M. (1998). Rheumatoid arthritis. In P. J. Maddison, D. A. Isenberg, P. Woo, & D. N Glass. *Oxford Textbook of Rheumatology*, 2nd Ed., vol. 2. Oxford: Oxford University Press.
- Margolis, R. H. & Goycoolea, H. G. (1993). Multifrequency tympanometry in normal adults. *Ear and Hearing*, 14, 408-13.
- Margolis, R. H. & Heller, J. (1987). Screening tympanometry: Criteria for medical referral. *Audiology*, 26, 197-208.
- Margolis, R. H., Saly, G. L., & Hunter, L. L. (2000). High-frequency hearing loss and wideband middle ear impedance in children with otitis media histories. *Ear and Hearing*, 21, 206-211.
- Margolis, R. H., Saly, G. L., & Keefe, D. H. (1999). Wideband reflectance tympanometry in normal adults. *The Journal of the Acoustical Society of America*, 106, 265-280.
- Margolis, R. H., Van Camp, K. J., Wilson, R. H., & Creten, W. L. (1985). Multifrequency tympanometry in normal ears. *Audiology*, 24, 44-53.
- McCabe, B. F. (1979). Autoimmune sensorineural hearing loss. *Annals of Otolology, Rhinology, and Laryngology*, 88, 585-589.
- Mimosa Acoustics. (2005). Hear ID wideband middle ear power analyzer wbMEPA 2005 manual (v. 3.1.8/v. 4.3.3.3). Champaign, IL: Author.

- Moffat, D. A., Ramsden, N. T., & Rosenberg, J. N. (1977). Otoadmittance measurements in patients with rheumatoid arthritis. *The Journal of Laryngology and Otology*, 91, 917-927.
- Moots, R. & Jones, N. (2004). *Rheumatoid arthritis: your questions answered*. Edinburgh: Churchill Livingstone.
- Moreland, L. W. (Ed.) (2004). *Rheumatology and Immunology Therapy: A to Z Essentials*. Italy: Springer-Verlag Berlin Heidelberg.
- Morrell, C. H., Gordon-Salant, S., Pearson, J. D., Brant, L. J., & Fozard, J. L. (1996). Age- and gender-specific reference ranges for hearing level and longitudinal changes in hearing level. *Journal of the Acoustical Society of America*, 100, 1949-1967.
- Mukerji, B., Estrem, S. A., & O'Sullivan, F. X. (1994). The challenge of sensorineural hearing loss in rheumatoid arthritis. *The Journal of Rheumatology*, 21, 1753-1757.
- Nores, J. M., & Bonfils, P. (1988). Rheumatoid arthritis and auto-immune hearing loss: A case study. *Clinical Rheumatology*, 7, 520-521.
- Nozza, R J., Bluestone, C.D., Kardatze, D. & Bachman R. (1992). Towards the validation of aural acoustic immittance measures for diagnosis of middle ear effusion in children. *Ear and Hearing*, 13, 442-453.
- Onusko, E. (2004). Tympanometry. *American Family Physician*, 50, 1713-1717.
- Özcan, M., Karakus, M. F., Gündüz, O. H., Tuncel, Ü., & Sahin, H. (2002). Hearing loss and middle ear involvement in rheumatoid arthritis. *Rheumatology International*, 22, 16-19.

- Öztürk, A., Yalçın, Ş., Kaygusuz, İ., Şahin, S., Gök, Ü., Karlidağ, T., & Ardiçoğlu, Ö. (2004). High-frequency hearing loss and middle ear involvement in rheumatoid arthritis. *American Journal of Otolaryngology*, 25, 411-417.
- Papadimitraki, E. D., Kyrmizakis, D. E., Kritikos, I., & Boumpas, D. T. (2004). Ear-nose-throat manifestations of autoimmune rheumatic diseases. *Clinical and Experimental Rheumatology*, 22, 485-494.
- Piskorski, P., Keefe, D. H., Simmons, J. L., & Gorga, M. P. (1999). Prediction of conductive hearing loss based on acoustic ear canal response using a multivariate clinical decision theory. *Journal of the Acoustical Society of America*, 105, 1749-1764.
- Pugh, M. B. et al. (Eds). (2000). *Stedman's Medical Dictionary* (27th ed.). Philadelphia: Lippincott Williams & Wilkins.
- Raut, V. V., Cullen, J., & Cathers, G. (2001). Hearing loss in rheumatoid arthritis. *The Journal of Otolaryngology*, 30, 289-294.
- Reiter, D., Konkle, D. R., Myers, A. R., Schimmer, B., & Sugar, J. O. (1980). Middle ear immittance in rheumatoid arthritis. *Archives of Otolaryngology*, 106, 114-117.
- Rigual, N. R. (1988). Otolaryngologic manifestations of rheumatoid arthritis. *Ear, Nose & Throat Journal*, 66, 436-439.
- Rosenberg, J. N., Moffat, D. A., Ramsden, R. T., Gibson, W. P. R., & Booth, J. B. (1978). Middle ear function in rheumatoid arthritis. *Annals of the Rheumatic Diseases*, 37, 522-524.

- Salvinelli, F., Cancilleri, F., Casale, M., Luccarelli, V., Di Peco, V., D'Ascanio, L., De Martino, A., & Denaro, V. (2004). Hearing thresholds in patients affected by rheumatoid arthritis. *Clinical Otolaryngology and Allied Sciences*, 29, 75-79.
- Salvinelli, F., D'Ascanio, L., Casale, M., Vadacca, M., Rigon, A., & Afeltra, A. (2006). Auditory pathway in rheumatoid arthritis. A comparative study and surgical perspectives. *Acta Oto-Laryngologica*, 126, 32-36.
- Sesterhenn, G. & Breuninger, H. (1978). On the influence of the middle ear muscles upon changes in sound transmission. *Archives of Otorhinolaryngology*, 221, 47-60.
- Shahnaz, N. & Bork, K. (2006). Wideband reflectance norms for Caucasian and Chinese young adults. *Ear and Hearing*, 27, 774-788.
- Shahnaz, N. & Davies, D. (2006). Standard and multi-frequency tympanometric norms for Caucasian and Chinese young adults. *Ear and Hearing*, 27, 75-90.
- Shahnaz, N. & Polka, L. (1997). Standard and multifrequency tympanometry in normal and otosclerotic ears. *Ear and Hearing*, 18, 326-341.
- Shanks, J. E. (1984). Tympanometry. *Ear and Hearing*, 5, 268 – 280.
- Shanks, J. E., Lilly, D. J., Margolis, R. H., Wiley, T. L., & Wilson, R. H. (1988). Tutorial: tympanometry. *Journal of Speech and Haring Disorders*, 53, 354-377.
- Shanks, J. E. & Shelton, C. (1991). Basic principles and clinical applications of tympanometry. *Otolaryngology Clinics of North America*, 24, 299 – 328.

- Shanks, J. E., Wilson, R. H., & Cambron, N. K. (1993). Multiple frequency tympanometry: effects of ear canal volume compensation on static acoustic admittance and estimates of middle ear resonance. *Journal of Speech and Hearing Research, 26*, 178-185.
- Siamopoulou-Mavridou, A., Asimakopoulos, D. Mavridis, A., Skevas, A., & Moutsopoulos, H. M. (1990). Middle ear function in patients with juvenile chronic arthritis. *Annals of the Rheumatic Diseases, 49*, 620-623.
- Silman, A. J. (1988). The 1987 revised American rheumatism association criteria for rheumatoid arthritis. *British Journal of Rheumatology, 27*, 341-343.
- Silman, A. J. (2001). Rheumatoid arthritis. In A. J. Silman & M. C. Hochberg (Eds.) *Epidemiology of the Rheumatic Diseases*, (pp.31-71). New York: Oxford University Press.
- Steinbrocker, O., Traeger, C. H., & Batterman, R. C. Therapeutic criteria in rheumatoid arthritis. *Journal of the American Medical Association, 140*, 659-662.
- Street, I., Jobanputra, P., & Proops, D. W. (2006). Etanercept, a tumor necrosis factor α receptor antagonist, and methotrexate in acute sensorineural hearing loss. *The Journal of Laryngology and Otology, 120*, 1064-1066.
- Takatsu, M., Higaki, M., Kinoshita, H., Mizushima, Y., & Koizuka, I. (2005). Ear involvement in patients with rheumatoid arthritis. *Otology and Neurotology, 26*, 755-761.

- U.S. Department of Health and Human Services: National Institute of Arthritis and Musculoskeletal and Skin Diseases. (2004). *Rheumatoid arthritis*. (NIH Publication No. 04-4179). Bethesda, MD.
- Valvik, B. R., Johnsen, M. & Laukli, E. (1994). Multifrequency tympanometry. Preliminary experiences with a commercially available middle-ear analyzer. *Audiology*, 33, 245-53.
- Van Camp, K. J., Margolis, R. H., Wilson, R. H., Creten, W. L., Shanks, J. E. (1986). Principles of tympanometry. *American Speech-Language Hearing Association Monograph*, 24, 1-88.
- Vander Werff, K. R. & Prieve, B. A. (2004, Feb.). Test-retest reliability of wide-band reflectance measures in infants. 27th Annual Midwinter Meeting of the Association for Research in Otolaryngology, Daytona Beach, FL.
- Vanhuyse, V. J., Creten, W. L., & Van Camp, K. J. (1975). On the W-notching of tympanograms. *Scandinavian Audiology*, 4, 45-50.
- Voss, S. E., & Allen, J. B. (1994). Measurement of acoustic impedance and reflectance in the human ear canal. *Journal of the Acoustical Society of America*, 95, 372-384.
- Voulgari, P. V., Papazisi, D., Bai, M. Zagorianakou, P., Assimakopoulos, & Drosos, A. A. (2005, March 11). Laryngeal involvement in rheumatoid arthritis. *Rheumatology International*, Retrieved May 20, 2005, from <http://spingerlink.com>.

Wiley, T. L., Cruickshanks, K. J., Nondahl, D. M., & Tweed, T. S. (1999). Aging and middle ear resonance. *Journal of the American Academy of Audiology*, *10*, 173-179.

Wiley, T. L. & Stoppenbach, D. T. (2002). Basic principles of acoustic immittance measures. In J. Katz (ed.) *Handbook of Clinical Audiology*, 5th ed. Philadelphia: Lippincott Williams & Wilkins.

Zwislocki, J. (1963). An acoustic method for clinical examination of the ear. *Journal of Speech and Hearing Research*, *6*, 303-314.