2009

**Autonomic dysfunction in patients with migraine associated dizziness (MAD)**

Lauren Tegel

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Abstract: The goal of this project is to identify what effect vestibular stimulation has on the reaction of the autonomic nervous system, as measured by blood pressure, blood-oxygen saturation levels, and heart rate monitoring, on subjects with migraine associated dizziness (MAD) as compared to healthy non-MAD subjects.
I would like to thank the following people for their contributions and hard work in helping me complete this Capstone project. The aid and support that these people have given to this project are innumerable and immense.

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>ii</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>2</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>3</td>
</tr>
<tr>
<td>Appendix A</td>
<td></td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>4</td>
</tr>
<tr>
<td>Appendix B</td>
<td></td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>7</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>8</td>
</tr>
<tr>
<td>METHODS</td>
<td>22</td>
</tr>
<tr>
<td>RESULTS</td>
<td>27</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>35</td>
</tr>
<tr>
<td>CONCLUSION</td>
<td>37</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>38</td>
</tr>
<tr>
<td>APPENDICES</td>
<td></td>
</tr>
<tr>
<td>A    Descriptive Statistics for All Data</td>
<td>43</td>
</tr>
<tr>
<td>B    Graphs of All Data</td>
<td>47</td>
</tr>
</tbody>
</table>
LIST OF FIGURES

FIGURE 1:
Group Mean Comparisons of Diastolic Blood Pressure 24

FIGURE 2a:
Control Subject Comparisons of Heart Rate for Each Test 25

FIGURE 2b:
Experimental Subject Comparisons of Heart Rate for Each Test 25

FIGURE 3:
Group Mean Comparisons of Blood-Oxygen Saturation levels 26

FIGURE 4:
Group Mean Comparisons of Systolic Pressure 27

FIGURE 5:
Age- and Gender-Matched Comparisons of Blood Pressure 28

FIGURE 6:
Age- and Gender-Matched Subject Set of Heart Rate Comparisons 29
LIST OF TABLES

APPENDIX A

TABLE A: 43
Descriptive Statistics of Diastolic Pressure for Group Comparisons

TABLE B: 43
Descriptive Statistics of Systolic Pressure for Group Comparisons

TABLE C: 44
Descriptive Statistics of Heart Rate for Group Comparisons

TABLE D: 44
Descriptive Statistics of Blood-Oxygen Saturation Levels for Group Comparisons

TABLE E: 45
Descriptive Statistics of Diastolic Pressure for Age- and Gender-Matched Groups

TABLE F: 45
Descriptive Statistics of Systolic Pressure for Age- and Gender-Matched Groups

TABLE G: 46
Descriptive Statistics of Heart Rate for Age- and Gender-Matched Groups

TABLE H: 46
Descriptive Statistics of Blood-Oxygen Saturation Levels for Age- and Gender-Matched Groups
LIST OF FIGURES

APPENDIX B

Group Comparisons

FIGURE 1: 47
Blood-Oxygen Saturation Levels for Sensory Organization Testing

FIGURE 2: 48
Blood-Oxygen Saturation Levels for Rotational Chair Testing

FIGURE 3: 48
Blood-Oxygen Saturation Level Fluctuations for Sensory Organization Testing

FIGURE 4: 49
Blood-Oxygen Saturation Level Fluctuations for Rotational Chair Testing

FIGURE 5: 49
Diastolic Pressure for Sensory Organization Testing

FIGURE 6: 50
Diastolic Pressure for Rotational Chair Testing

FIGURE 7: 50
Diastolic Pressure Fluctuations for Sensory Organization Testing

FIGURE 8: 51
Diastolic Pressure Fluctuations for Rotational Chair Testing

FIGURE 9: 51
Systolic Pressure for Sensory Organization Testing

FIGURE 10: 52
Systolic Pressure for Rotational Chair Testing
FIGURE 11:  
Systolic Pressure Fluctuations for Sensory Organization Testing

FIGURE 12:  
Systolic Pressure Fluctuations for Rotational Chair Testing

FIGURE 13:  
Heart Rate for Sensory Organization Testing

FIGURE 14:  
Heart Rate for Rotational Chair Testing

FIGURE 15:  
Heart Rate Fluctuations for Sensory Organization Testing

FIGURE 16:  
Heart Rate Fluctuations for Rotational Chair Testing

Age-and Gender Matched Comparisons

FIGURE 17:  
Heart Rate Comparisons for Experimental Subject 4 and Control Subject 11

FIGURE 18:  
Heart Rate Comparisons for Experimental Subject 6 and Control Subject 9

FIGURE 19:  
Diastolic Pressure Comparisons for Experimental Subject 2 and Control Subject 13

FIGURE 20:  

Systolic Pressure Comparisons for Experimental Subject 2 and Control Subject 13

FIGURE 21: 58

Diastolic Pressure Comparisons for Experimental Subject 4 and Control Subject 11

FIGURE 22: 58

Systolic Pressure Comparisons for Experimental Subject 4 and Control Subject 11

FIGURE 23: 59

Diastolic Pressure Comparisons for Experimental Subject 6 and Control Subject 9

FIGURE 24: 59

Systolic Pressure Comparisons for Experimental Subject 6 and Control Subject 9
LIST OF ABBREVIATIONS

IHS- International Headache Society
CDP- Computerized Dynamic Posturography
RC- Rotational Chair
VVOR- Visual- Vestibular Ocular Reflex
VOR- Vestibular Ocular Reflex
OPK- Optokinetics
GPRD- General Practice Research Database
MSNA- Muscle Sympathetic Nervous Activity
MAD- Migraine Associated Dizziness
AD- Anno Domini
PET- Positron Emission Tomography
MRI- Magnetic Resonance Imaging
DT- MRI- Diffusion Tensor Magnetic Resonance Imaging
BA- Brodmann's Area
SNP- Single Nucleo-Peptide
PGR- Progesterone Receptor
CNS- Central Nervous System
ANS- Autonomic Nervous System
TIA- Transient Ischemic Attack
mmHg- millimeters in mercury
bpm- Beats per Minute
INTRODUCTION AND LITERATURE REVIEW

Migraines are recurring neurological events which involve blood vessels, nerves, and chemical reactions in the brain and in many other areas of the body. Generally, headaches are the most frequent presentation of these events. However, migrainous events are not restricted to the perception of headaches. In fact, a variety of anatomical areas are affected by these neurological events. The gastrointestinal, retinal, vascular, and vestibular systems all show adverse effects of migrainous neurologic involvement in current literature. These systems may be affected with the inclusion of, or completely devoid of, the perception of a headache. The International Headache Society (IHS) is the current governing body that defines the criteria for diagnosing any type of primary or secondary migraine. Currently, the IHS accepts primary migraine types to include: common migraines without aura, classic migraines with aura, basilar-type migraines, hemiplegic migraines, retinal or ophthalmic migraines, and abdominal migraines. The IHS only recognizes vestibular migrainous symptoms in relation to a primary basilar-type migraine or as a secondary migraine in relation to specific genetic disorders. Similarly, the IHS recognizes a vascular migrainous component only in the realm of migraine secondary to an ischemic stroke or specific genetic syndromes (Lance and Olsen, 2004). Migraine associated dizziness (MAD) is currently not addressed or defined by the IHS, even though it is one of the most common reasons a patient will visit a dizziness and balance clinic (Neuhauser et al., 2001). Although the IHS recognizes a vestibular component in the diagnosis of a primary basilar-type migraine, the vestibular component, in addition to light, sound, and motion sensitivity, is insufficient for a basilar-type migraine diagnosis. The criteria for a basilar-type migraine presents with a
symptomatology of dysarthria, ataxia, decreased level of consciousness, diplopia, hyperacusia, tinnitus, simultaneous visual symptoms in the temporal and nasal fields, and simultaneous bilateral paraesthesias (Lance and Olsen, 2004). Most patients with MAD do not present these symptoms unless the MAD is secondary to another disorder. Therefore, patients presenting with MAD do not necessarily meet the IHS's criteria for primary migraine (Furman et al., 2003; Kayan and Hood, 1984). Without this concrete diagnostic criterion of MAD, investigators have traditionally used operational definitions of MAD based on the symptomatology presented. Symptoms of MAD, as previously mentioned, are similar to those presented in the classic migraine; they include bouts of dizziness, nausea, vomiting and hypersensitivity to light, sound, motion, and nausea.

Migraine associated dizziness was operationally defined by Neuhauser et al. (2001), as a "vestibular syndrome caused by migraine, that presents with attacks of spontaneous or positional vertigo lasting seconds to days in conjunction with migrainous symptoms during the attack." They went on to report that migraine associated dizziness is the most common cause of spontaneous recurrent vertigo (Neuhauser et al., 2001). More recently, Brandt (2006) reported diagnosing MAD based on his criteria of “spontaneous recurrent attacks of vertigo/dizziness (prevailing type rotational) most often lasting minutes to hours associated with headache or other migrainous symptoms and in the majority an individual history of migraine according to the International Headache Society (IHS) criteria” after his review of current literature.

"The association of disorders of hearing and balance with migraine has been recognized as early as AD 131", according to Kayan and Hood (1984). However, the authors continue to report that "it was Liveing in 1873 who was the first to draw attention
to the clear association of vertigo with migraine." Since the early days of discovery, few studies have been undertaken that directly examine the MAD population. Studies directed at the MAD population have evaluated the epidemiology, the pathophysiology, and the diagnostic results of this disorder. These epidemiologic studies have shown relative frequency of vestibular components to migraine events. The first popular and large population-based epidemiological study was produced by Kayan and Hood in 1984. That analysis included 200 patients with migrainous symptoms with vestibular components, defined as vertigo and phonophobia, and was performed using a control group consisting of 200 tension headache counterparts. The subjects surveyed had a higher prevalence of vestibular symptoms: 57% of the migraine group demonstrated these symptoms as compared with 31% of the tension group (Kayan and Hood, 1984).

Neuhauser et al. (2001) undertook a prospective investigation and evaluated 200 consecutive patients from a dizziness clinic and 200 patients from a migraine clinic for migrainous vertigo. The authors also compared the prevalence of migraine, according to IHS criteria, in the dizziness clinic group with a sex- and age-matched control group of 200 orthopedic patients. The results substantiated the epidemiologic association between migraine and vertigo and indicated that migrainous vertigo had affected a significant proportion of patients in dizziness and headache clinics. Specifically, the prevalence of migraine, according to IHS criteria, was 1.6 times higher in the 200 dizziness clinic patients than in 200 sex- and age-matched controls from an orthopedic clinic (Neuhauser et al., 2001). A more recent investigation, completed by Vukovic et al. (2007), also reported that the lifetime prevalence of migrainous vertigo is relatively frequent in migraine patients, especially in patients with classic migraine. Their study included 327
migraine patients and 324 control subjects, who did not suffer from frequent headaches. Vertigo or dizziness was experienced by 51.7% of migraine patients and 31.5% in the control group. Patients with migraine preceded by aura had migraine attacks significantly more often in association with vertigo or dizziness. Nandi and Luxon (2008) found that patients presenting with vertigo had a 30% to 50% prevalence rate of migraine. In 2001, Weisleder and Fife reported 35% of referred children were diagnosed with a "vestibular migraine" or its equivalent in the Balance Center at the Barrow Neurological Institute. The authors examined charts of 31 children, and 11 of them received a diagnosis of vestibular migraines. Of those 11 patients, three were male and eight were female. There were six with a family history of migraine, five had a history of motion sickness, seven had no abnormality in the tests for vestibular function, and eight underwent additional diagnostic procedures. The authors noted that their population was small, but felt that their findings were in agreement with other papers which stated that vestibular migraine was the most common diagnosis assigned to patients. A study by Wiener-Vacher (2008) supported Weisleder and Fife's finding and published similar results from her evaluation of 2000 children referred for vertigo and balance disorders to the Functional Vestibular Evaluation Unit of the ENT Pediatric Department at Robert Debre’ Hospital in Paris, France. She found that "among the diagnoses put forward for children with vertigo, the most frequent is migrainous equivalent at a rate of 25%: The vertigo was associated with headaches."

Similar to the defining criteria of MAD, the current pathophysiology and etiology of the disorder has also been unaccounted for and underexamined in published studies.
Therefore, the classic migraine serves as a model for this study, with the understanding that the two disorders have been linked by an unknown process.

Several theories have been accepted by professionals as possible disease pathways and etiologies of migraines. The classic vascular theory has been popular and generally accepted in the neurological community. This theory surmised that the perceived aura and headache were due to vasospams in brain tissue until imaging studies found that cerebral vascular changes did not parallel with onset of aura and headache (Vincent and Hadjikhani, 2007). Neuronal excitation has also been purported as a possible etiology of migraines. This theory hypothesizes "a lower neuronal preactivation level whereby neurons are more readily able to fire." This lower preactivation level sets the system up for hyperexcitabile responses to incoming stimuli and has been supported in some literature (Vincent and Hadjikhani, 2007). Another hypothesis that has been proposed includes cortical spreading depression in the area of Leao. This theory was best described as "a spreading wave of depolarization associated with a reduction of the cortical activity which lasts for minutes with a propagation speed of around 3 mm/min" and is supported by functional imaging studies (Vincent and Hadjikhani, 2007). In a review paper by Furman, Marcus, and Balaban (2003), several lesser known theories were reviewed. The authors described possible variations in neurotransmitter levels of serotonin and norepinephrine, a trigeminal sensory–parasympathetic reflex, and substance P (a pro-inflammatory neuropeptide that causes vasodilatation and extravasation) release from trigeminal sensory terminals as possible physiologic pathway complications (Vass et al., 2004; Furman et al., 2003). An interesting study published in 2007 used positron emission technology (PET) to visualize spontaneous activation in...
hypothalamic areas. This was completed during acute migraine attacks, as compared to the headache-free PET scans; several comparisons were made. The authors were able to observe significant activations of the hypothalamus and several brainstem areas: specifically, the bilateral ventral midbrain, dorsal midbrain contralateral to the headache, and the dorso-medial pons. Activations during headache were also seen in both cerebellar hemispheres, fronto-inferior cortex ipsilateral to the headache (Brodmann areas [BA] 47, 13), and inferior anterocaudal cingulate cortex contralateral to the headache (BA 25) (Denuelle, Fabre, and Geraud, 2007). This investigation successfully produced imaging showing hypothalamic activity during migraine attacks. Another study examined an etiology that has been supported by the gender differences in prevalence rates. In 2007, Lee and colleagues investigated two genetic variations in the MAD population. They compared an estrogen receptor and a progesterone receptor and found a genetic variant that was significantly associated with MAD. The PROGINS variant of the SNP, single nucleo-peptide (rs1042838 T- allele), on the progesterone receptor (PGR) was found to have a significant association to MAD. Subjects with this variation were twice as likely to have MAD. This finding could not be generalized to the male participants in this study due to the high female to male ratio in all subgroups (5:1) and the small sample set of male-only groups. Finally, the theory of most significance for this paper is one of autonomic dysfunction. This theory examines the physical symptoms of migraine and the systems that regulate and connect the areas of presentation. The physical symptoms most illustrative of the connections between migraine, MAD, and autonomic connection are the emetic response, nausea, and motion intolerance. A case has been made for the light reflex sensitivity in migraineurs as compared to a control.
group. In 2003, Mylius and colleagues examined pupillary light reflex in a group of 42
migraineurs and 42 non-migrainous subjects. They found that subjects with a migraine
two days prior to testing had a lower dilatation velocity on both eyes as compared to the
headache-free control group.

The autonomic nervous system (ANS) is a combination of two antagonistic
systems: the sympathetic and parasympathetic nervous systems. These systems work
together to maintain homeostasis in the body without conscious control. The ANS is
predominantly an efferent system that affects control of heart rate and force of
contraction, constriction and dilatation of blood vessels, contraction and relaxation of
smooth muscle in various organs, visual accommodation, pupillary size and secretions
from exocrine and endocrine glands. Autonomic nerves constitute all of the efferent
fibers which leave the central nervous system (CNS), except for those that innervate
skeletal muscle. There are some afferent autonomic fibers which are concerned with the
mediation of visceral sensation and regulation of vasomotor and respiratory reflexes.
Some examples are the baroreceptors and chemoreceptors in the carotid sinus and aortic
arch, which are important in the control of heart rate, blood pressure and respiratory
activity. These afferent fibers are usually carried to the CNS by major autonomic nerves
such as the vagus, splanchnic, or pelvic.

The ANS aids in heart rate and blood pressure regulation by integrating
information from arterial baroreceptors and other inputs to make necessary adjustments
to the heart and vascular smooth muscle with the purpose of maintaining a steady-state
blood pressure. The sympathetic process regulates the "fight-or-flight" response: pupils
dilate, muscle vasculature dilates, heart rate increases, and the digestive system is put on
The parasympathetic process helps the body to return to resting state after the sympathetic system runs its course. This process includes decreasing heart rate and blood flow by slowing down the cardiac muscle contractions, constricting the pupils, and stimulating the gut and salivary glands.

The ANS supplies information to the heart, arteries, veins, lungs, gastro-intestinal tract, liver, kidney, bladder, uterus, eye, and salivary glands. The sympathetic system is thought to originate from the cells of the intermediolateral column in the thoracic spinal cord. Then they travel to ganglia before reaching the target organ. Some notable ganglia that receive sympathetics include: the superior cervical ganglion, which dilates the pupils, stimulates sweat glands, and lifts the eyelids; the celiac and mesenteric ganglia, which distribute sympathetics to the gut to create vasoconstriction and inhibit secretions; and the chain ganglia along the spinal cord serve as a distribution system for the sympathetics to the thorax and periphery to cause an increase heart rate, dilate bronchi, selectively vasoconstrict, and vasodilation in active muscles. Parasympathetic cells are located in different nuclei throughout the brainstem, as well as a few in the sacral spinal cord. Their axons travel to the target organ, synapse in ganglia in or near the organ wall, and finally innervate the organ. Examples of these ganglia include ciliary, otic, and pterygopalatine in the head, and a diffuse network of cells in the walls of the heart, gut, and bladder. The bodily responses include pupil constriction, lens accommodation, stimulation of gastric secretion, stimulation of gut motility, stimulation of respiratory secretions, decreased heart rate, and bronchial constriction.

Several studies have shown a connection between the vestibular system and the autonomic system via blood pressure and heart rate regulation measurements. Doba and
Reis provided a provocative study in 1974 that showed a bilateral VIIIth nerve section compromised the ability of anesthetized cats to adjust blood pressure during orthostatic challenge by nose up tilt. They proposed a contribution of vestibular inputs to baroreceptor reflexes that regulate blood pressure and volume distribution during changes of body posture. More recently, Wilson and colleagues (2006) studied cats and electrical or natural stimulation of vestibular receptors. They found that stimulation elicits changes in the activity of sympathetic efferents, particularly vasoconstrictor fibers. In human subjects, modulation of vestibular nerve activity has been achieved through head-down neck flexion, bi-thermal caloric stimulation of the ear, and off-vertical axis rotation. It has been shown that these vestibular-stimulating movements were also able to alter sympathetic nerve firing in humans as measured in subdermal needle electrodes embedded in muscles, on electrocardiograms, by using cardiac catheters, and by plethysmography. (Lee et al., 2001; Mori et al., 2005; Ray and Hume, 1998; Kaufmann et al, 2002). In addition to the common reaction of these maneuvers, a study by Cooke and colleagues (2004) found that head-down rotation independently activated the sympathetic nervous system, with no effect on parasympathetic activity. In addition to these activations, they also found that the frequency-dependent associations between arterial pressures and parasympathetic activity were independent of vestibular activation. These findings supported a connection of the vestibular system to the autonomic system, which interact independently of each other and redundantly together to maintain steady-state hemodynamics. Yates and Bronstein (2005) found that "removal of vestibular inputs only resulted in an inability to rapidly adjust blood pressure during postural alterations when animals were tested in the absence of visual cues that could be employed to detect
body position in space." The combination of these studies implicated that subjects without vestibular impairment would be able to maintain blood pressure and regulate heart rate. This body of literature also suggested that head-down neck flexions, caloric stimulation of the ear, and off-vertical axis rotation should not be used for this current study because these tests could cause physiologic fluctuations in both groups yielding insignificant data.

Vestibular inputs were not the only implication that an autonomic disturbance could be the root of symptomatology in subjects with MAD and migraine. A body of research examined connections between migraines with and without aura, cardiovascular, and cerebrovascular pathologies in order to explain the epidemiologic links found in several studies. One epidemiologic study was published in 2007 by Becker et al. This study looked at the connection between migraines and stroke by using the United Kingdom's General Practice Research Database (GPRD). The investigators viewed a sample of people 79 years old or younger, with at least three years of medical history in the database record prior to their first-time migraine diagnosis. From this sample, an equally sized comparison group of individuals without migraine, identified randomly from the study sample, was matched to migraineurs on age (year), gender, general practice, history on the GPRD, and date of the first migraine diagnosis recorded. Parameters were defined as all persons who had an incident diagnosis of thrombotic or hemorrhagic stroke, a transient ischemic attack (TIA), or who died between the time of the first migraine diagnosis and the end of the study period. All patients who had a history of stroke or TIA prior to their first recorded migraine diagnosis and all patients with a history of cancer were excluded. All electronic records were manually reviewed
blind of exposure issues. The study included a total of 103,376 individuals: 51,688 migraineurs and 51,688 matched persons without a diagnosed migraine. When they evaluated all stroke events among the groups, they found that the migraine group yielded a relative risk of 2.2 times higher than the matched control group. Transient ischemic attacks were found 2.4 times more often in the migraine group than the control group (Becker et al., 2007). Another large population study, undertaken by Kurth and colleagues (2006), used data from a previous Women's Health Study sponsored by the National Heart, Lung, and Blood Institute. The authors reported that the initial study did not find that migraine was associated with coronary heart disease after a mean of six years of follow-up. The investigators re-evaluated the data after a mean of 10 years follow-up on the subset migraine group. The follow-up group yielded a population of 3,610 migraine subjects, 39.7% of which reported aura. The study used the non-migraine reporting population as their control group. After adjusting for age, the classic migraine group was found to have an increased risk for cardiovascular disease (1.7 times). The groups were matched based on cardiovascular risk assessment of factors such as smoking, hypertension, age, and obesity.

With these and other studies correlating migraine and vascular events, a number of studies delved into a revival of exposing the anatomy and physiology of migraines as compared to non-migraine counterparts. Some of these studies have succeeded in establishing a correlation between migraine and vascular events. Specifically, de Hoon et al. (2003) found that subjects with migraine had an increase in peripheral arterial wall stiffness and an increase in right temporal artery diameter. These authors examined a group of 50 migraine subjects and a group of 50 gender, age, body mass index, blood
pressure, cholesterol and smoking habit matched subjects. They assessed pressure waveforms, pulse pressures, vessel wall movements, vessel wall properties, blood flow, vascular resistance, cardiac output with a pulsed ultrasound, and systemic vascular resistance. The only variables that were found to be significantly different between groups were an increase in peripheral arterial wall stiffness and an increase in right temporal artery diameter. The authors concluded that their study implicated a more widespread pathophysiology of migraines. In another successful study, diffusion tensor magnetic resonance imaging (DT-MRI) was used to identify pathological damage of normal appearing brain tissue from patients with migraine. The authors found a significant difference in the presentation of white matter damage between the group of 34 migraineurs and 17 participants in the non-migraine group (Rocca et al., 2003). Another investigation, lead by Kruit (2004), evaluated magnetic resonance imaging (MRI) of subjects with migraine and compared the images to subjects without migraines. This study reported finding no increase or decrease in the white matter on the MRI; however, the authors did report an increase in risk of posterior circulation territory infarcts in the group defined as classic migraine only.

Several physical connections between migraine and the autonomic nervous system have been recognized. Since MAD has not yet been thoroughly studied and epidemiologic links have been found in migraines and MAD, it is assumed for the purposes of this study, that the links between migraines and the autonomic nervous system must be similar to links between MAD and ANS. Physical connections between migraine, MAD, and ANS include the emetic response elicited during bi-thermal caloric
irrigation, blood pressure changes in hand grip tests (Peroutka, 2003), light sensitivity, throbbing headaches, and often complaints of fatigue and poor concentration.

In addition to the previously mentioned animal and human studies connecting migraines, dizziness, and autonomic responses, it is imperative to look at the clinical findings from previous research studies. Studies have looked at visual-vestibular ocular reflex (VVOR), computerized dynamic posturography (CDP), bi-thermal caloric irrigation, and optokinetics in subjects with migraines, migraine associated dizziness, and normal population control subjects. Arriaga et al. (2006) found that VVOR gain was more frequently elevated in "migraine vestibulopathy" patients than in the normal controls and the difference was significant. VVOR gain elevation was the most common vestibular test abnormality in this cohort of patients with "migraine vestibulopathy". Because VVOR measures the visual-vestibular interaction and its central connections, this parameter may be a useful diagnostic tool for MAD patients manifesting disequilibrium and motion sensitivity. Seventy-one percent of the patients diagnosed with "migraine vestibulopathy" in this retrospective clinical study had abnormally high gain on VVOR.

Celebisoy et al. (2008) showed that static CDP results from people with migraine associated vertigo revealed more sway velocity when the eyes were closed or the platform was distorted. Celebisoy published another study in 2008 with more vestibular testing results for subjects with MAD. These subjects demonstrated an excessive reliance on somatosensation for upright balance. None of the patients with migraine had ocular motor abnormalities such as saccadic inaccuracy, saccadic pursuit or impaired optokinetic nystagmus. However, within the MAD group there were three patients with
saccadic pursuit (8.6%), and one of whom saccadic hypometria was also present. Bithermal caloric test results were normal in all patients within the migraine group; whereas in the MAD group, there were seven patients (20%) with unilateral caloric hypofunction. Crevits and Bosman (2005) reported that "as yet, no laboratory investigation has been found to be specific enough to be considered diagnostic" with regards to patients demonstrating MAD. This finding has held true in the literature since the publication in 2005. In 2007, Vitkovic and colleagues completed a study of 523 subjects and potentially identified that the emetic response to bi-thermal caloric stimulation may have been a distinguishing factor between migrainous vertigo and other vestibular disorders, including those with a coexisting history of migraine.

The theory behind the current study was based on the symptoms of MAD being generated from a defective autonomic system. The tested hypothesis states that the hypersensitive nature of MAD will not be specific to only light, sound, and motion but will also include changes in the vestibular system as shown with the measurement of physiologic responses of the autonomic system. To illustrate this, blood pressure (systolic and diastolic), blood–oxygen saturation levels and heart rate were measured throughout vestibular testing.
METHODS

This experiment assessed physiologic responses during vestibular testing in subjects with MAD and compared them to the results of a control group without MAD. In order to complete this experiment, two groups of subjects were recruited. The control group was comprised of eight participants (n=8), seven female and one male, with a mean age of 37.38 years and a median age of 37 years. The range of ages in the control group was from 23 to 51 years of age. The error was calculated at 4.18. The control group also consisted of a subset of participants that were age- and gender-matched to the experimental group. This group consisted of two females and one male, with a mean age of 32.33 years and a median age of 34 years. The ages ranged from 23 to 45 years. The error of this group was calculated at 4.98. Both groups were defined by the absence of: a MAD diagnosis, a baseline blood pressure above or below the normal range (normal range was defined as 90/60 to 140/90), previous dizziness/imbalance, and previous use of testing equipment. The experimental group consisted of three participants (n=3): two females and one male, with a mean age of 34.67 and a median age of 37 years. The ages ranged from 22 to 40 years. The error was 6.74. This group was defined using a previous diagnosis of MAD. All patients were recruited from the Dizziness and Balance Center at The Center for Advanced Medicine, a Washington University School of Medicine affiliate, and the surrounding metropolitan area. Participation was on a volunteer-only basis. All subjects gave their informed consent before entering the study, which was approved by Washington University School of Medicine Human Research Protection Office Institutional Review Board (IRB no. 08-1168). The general inclusion criterion was restricted to adults, both male and female, ages 21 to 85 years. All control
subjects were ambulatory with no major musculoskeletal deficits and no prior history of inner ear or balance disturbance. All experimental subjects were ambulatory with no major musculoskeletal deficits. The exclusion criteria eliminated subjects if they were cognitively impaired, had major musculoskeletal deficits, were pregnant, or under the age of 21 years. Subjects with a history of hypertension or who were currently being treated for hypertension were also excluded from the study.

Four tests were administered to both groups of participants: sensory organization test (SOT), vestibular ocular reflex (VOR), visual-vestibular ocular reflex (VVOR), and optokinetics (OPKs). The testing procedures utilized for this study were novel to all of the participating subjects. In all of the tests the subjects were secured in either a safety harness or a chair. Each subject read and signed an informed consent form and were given a copy to keep for his or her personal records. Each subject was verbally notified of the activities included in this study, the meaning of the informed consent form, and that he or she may decide to cease testing procedures at any time. Subjects in both groups were asked to sit down and relax for approximately five minutes while they read the informed consent form. After the subjects read the form, a baseline measurement of their blood pressure, heart rate, and oxygen saturation levels was taken (Baseline-0). Diastolic and systolic blood pressures were measured in millimeters of mercury (mmHg) using a LifeSource UA 767 Plus automatic blood pressure monitoring device. Diastolic pressure refers to the force of flow on the arterial wall while the heart is at rest. Systolic pressure relates to the amount of force applied to the arterial wall while the heart is beating. Heart rate, in beats per minute (bpm), and blood-oxygen saturation levels (in
percentage) were obtained with a TuffStat PSS Select pulse-oximeter. The tasking order for all subjects was randomized using a randomization generator.

Each subject performed the sensory organization test (SOT). This included a series of six subtests that utilized the NeuroCom computerized dynamic posturography platform (CDP) (NeuroCom International, Inc, Clackamas, OR, USA) to isolate and quantify the specific sensory inputs a person uses to keep his or her balance: the visual system, the vestibular system, and the somatosensory system or proprioception. The intervals for the SOT were broken up into three parts for obtaining measurements: before the first condition, while the subject stood on the platform in the harness (Baseline-SOT); after the third condition (SOT 1-3); and after the sixth condition (SOT 4-6). Each of the six conditions for the SOT procedure was repeated three times for approximately 20 seconds per trial. In the first subtest, the patient stood on the center of the platform with his or her eyes open directly in front of the visual surround. Everything remained completely still and the patient was able to use all sensory inputs to maintain stability. In the second condition, everything remained stable while the subject stood with his or her eyes closed. This removed the visual input, so the brain could only rely on the subject's proprioception and vestibular inputs. The first two subtests served as baselines for the interpretation and comparison of the remaining subtests. In the third subtest, the subject continued to face the visual surround with his or her eyes open and the platform remained stable. In this condition, the visual surround was sway-referenced, meaning that the visual surround moved proportionately to the subject's movement in direction and amplitude. The fourth subtest used a fixed visual surround and a sway-referenced platform. These sent competing messages to the brain from the proprioceptive and the
visual system. The fifth subtest was used to isolate the vestibular system from the other two systems. In this condition, the subject closed his or her eyes and the platform was referenced to the participant's movement or sway. In the last subtest, the subject had his or her eyes open and both the platform and the visual surround were sway-referenced. Physiologic measurements were obtained before the first subtest, while the subject was in the harness, and after the third and sixth subtests for a total of three measurement intervals during SOT.

For the VOR, VVOR, and OPK testing, the subject was seated and secured in a rotational chair (RC) (Micromedical Technologies, Inc, Chatham, IL, USA) that was enclosed in a booth with infrared video see-through-lenses secured to their head. The lenses were placed on the head so that the eyes' rapid movements could be watched and recorded.

During these tests, the participant was instructed to watch varying light projections and respond to simple questions (mental tasking) while the chair rotated on an earth-centered axis. Baseline physiologic measurements were taken while the subject was secured in the rotational chair (RC) and after each test. These tests stimulated the vestibular apparatus while tasking procedures kept the brain from fixating. Tasking procedures were defined as questions that were rapidly asked by the tester and rapidly answered by the subject. These questions were kept simple (i.e. naming months of the year, days of the week, types of animals, etc.) and were meant to keep the brain occupied for the purposes of this testing. Without mental tasking, the central system may compensate for the natural reaction of the vestibular system (suppression). If the subject suppressed the response, it may have obliterated or reduced the ocular reflex. The
combination of the testing procedures examined how each subject's vestibular and visual system functioned and interacted. The authors used these procedures to evaluate and compare physiologic responses to vestibular stimulation in both groups.

Due to the amount of testing and the need to observe and record accurate physiologic measurements (blood pressure, heart rate, and blood-oxygen saturation levels), it was pertinent to break up the process of obtaining responses into several intervals. The test intervals used for the RC were broken up into four measuring events: an initial measurement while seated in the RC (Baseline-RC), after VOR (RC-VOR), after VVOR (RC-VVOR), and after OPK (RC-OPK) testing. The batteries were broken up in a way that was optimal for recording purposes, least distracting for the participant, and optimal for vestibular testing that has shown promise for differential diagnosis of MAD and migraineurs in the previously studied literature.
RESULTS

Group comparisons were statistically analyzed utilizing the Mann-Whitney U test and the age- and gender-matched comparisons used the Wilcoxon test. These tests were utilized in order to reflect the non-normal distribution of the data. Statistical software, SPSS, was utilized for the calculations of both of these tests, as well as for the descriptive statistics. The standard error was calculated to range from 2.65 to 7.17 for systolic blood pressure measurements, from 2.16 to 4.41 for diastolic blood pressure measurements, from 1.82 to 12.50 for heart rate measurements, and from 0.49 to 0.78 for blood-oxygen saturation measurements. The confidence interval was set at 95%. For reference, tables of all descriptive statistics may be found in Appendix A. Due to the small subject pool, the generalization of the results and significance of the findings are limited. The data were analyzed with regard to group and age- and gender-matched comparisons. The age- and gender-matched assessments were completed in order to increase the power of this study. By using the age- and gender-matched groups for comparison, the power level of the study increased due to the elimination of some confounding variables such as, hormone levels and age-affected systemic changes in the cardiovascular system.

Each figure included in the text only displays post test measurement intervals that were found to best describe the authors' findings. Figures that display all findings that are not included in the text are located in Appendix B. The test intervals that were found to be statistically significant for the variable of diastolic blood pressure is displayed in Figure 1. The x-axis represents the test intervals (post test) at which physiologic measurements were taken. In this case, the physiologic variable was diastolic pressure.
The y-axis reflects the units of measurement that were attained during each interval. The diastolic measurements are blood pressure recordings that were obtained using a standard automatic blood pressure cuff and recorded in mmHg (a standard unit of measurement for blood pressure). The bars at the top of each column represent the 95% confidence interval. Test intervals, in which physiologic measurements were recorded, totaled eight.

The only test intervals that showed significant differences were: the baseline [measured while the subject stood on the posturography platform prior to SOT testing (BaselineSOT)], after completion of the sixth SOT condition (SOT4_6); and after the VOR test condition was complete (VOR). The significant comparative findings are denoted with an asterisk above the test interval bar. The graph for group comparisons displaying all test intervals is shown in Appendix B. The high rate of intra-group variability for heart rate as a physiologic response can be seen in Figures 2a and 2b. In both figures, the x-axes represent the test intervals at which heart rate were measured and the y-axes represent the heart rate in beats per minute (bpm). Figure 2a displays each
control subject's response for each interval and Figure 2b presents each experimental subject's response for each testing interval. Due to the previously mentioned
variability for this measurement, statistical significance could not be determined at any test interval. Blood-oxygen saturation levels were also not found to be statistically significant during any test interval.

Figure 3 depicts the general trend of the blood-oxygen saturation level data showing little-to-no difference between or within groups. Blood-oxygen saturation levels are represented by percentages (a standard unit of measurement for this variable) on the y-axis. On the x-axis, the test interval (post test) is listed. The bars represent the 95% confidence interval and the numbers in the middle of each column show the mean value or percentage for that test interval. The test intervals selected were measurements

**Group Comparisons for Mean Blood-Oxygen Saturation Levels**

![Figure 3. This graph depicts the between-group mean comparisons of blood-oxygen saturation levels for selected test intervals.](image)

30
obtained after the VOR test interval (RC-VOR) and a baseline, before any testing had transpired. These two intervals were selected for display because the change represented in this graph was the largest between-interval difference. Systolic pressure proved to be statistically significant during only two out of eight test intervals: SOT 1-3 (defined as measurements taken after the third SOT condition) and OPK (measurements obtained after OPK testing). Figure 4 illustrates the comparison between two measurements and denotes statistical significance with an asterisk (p<0.05). The test interval is on the x-axis. The first column represents the measurements obtained for systolic pressure

Group Comparisons of Mean Systolic Pressure

![Bar chart showing comparisons of mean systolic pressure between control and experimental groups. The chart indicates statistical significance with an asterisk.](image)

**Figure 4.** Between group comparisons for the variable of systolic blood pressure using one static test interval measurement and one dynamic measurement of the mean change in systolic pressure from the baseline to post-OPK measurements.
after the third SOT condition (a static measurement) and the second column represents the dynamic change in systolic blood pressure from the baseline to the measurement taken after OPK testing. This dynamic measurement was obtained by subtracting the value of the baseline from the measurement after OPK stimulation. The y-axis represents systolic blood pressure in mmHg.

Age- and gender-matched comparisons showed more of an approach toward statistical significance and maintained more consistent results. This could not be definitively determined due to a small subject number. Figure 5 shows the general trend of the mean differences in blood pressure measurements between the age- and gender-matched groups. The diastolic pressure is represented by the blue columns and the

![Matched Comparisons of Mean Blood Pressure](image-url)

*Figure 5. This graph compares the age- and gender-matched MAD subject to the control counterparts using blood pressure as the variable.*
systolic pressure is represented by the purple columns. The x-axis displays each experimental subject to the left of his or her control counterpart. The y-axis reports increments of blood pressure in mmHg.

Blood pressure measurements did show a consistent trend; however, heart rate measurements did not. One pair of the age- and gender-matched subjects showed a trend toward differentiation, but the other two pairs of matched subjects did not. Figure 6 shows the matched-pair group of an experimental and a control subject and the comparison of their heart rate over the span of the testing procedures. The x-axis displays the testing interval from the baseline through the OPK testing in the RC. The y-axis illustrates the units of measurement for heart rates. This graph depicts more frequent
and larger fluctuations in the heart rate of the MAD subject as compared to the control subject over the duration of the testing.

The bulk of the testing resulted in statistically non-significant results. This is thought to be due to the low power level (20% defined by a repeated analysis of variability) and small sample size of this study.
DISCUSSION

After reviewing the data and results of the control and experimental groups' physiological responses during testing, it was concluded that the results were variable. The authors were not able to provide generalized information for differentiating the experimental group from the control group in either the group or the age- and gender-matched comparisons. The few statistically significant findings yield promise for a larger study. A possibility still remains that statistical significance could be inflated due to multiple analyses. It is also necessary to report that the lack of significance could be due to investigator error, methods that are not sensitive enough for the measurements, and unaccounted extraneous variables. Investigator errors that may have infiltrated the data include, but are not limited to, the amount of time needed to take the physiological measurements and recording data. Both devices used to measure the physiologic responses were not instantaneous outputs and setting up for the measurements was not an instantaneous procedure. The variables assessed in this study require instantaneous measurements due to the body's naturally fast-acting regulatory system. This rapid regulatory system also implicates that the measurements used were not sensitive enough for accurate assessment of the variables. More sensitive and instantaneous monitoring devices would include those used in previous studies. Equipment in these studies often used more near-field monitoring techniques such as cardiac catheters, cardiotachometers, electrocardiography, ultrasound, and plethysmography (Doba and Ries, 1984; Kaufmann et al., 1998; Ray and Hume, 2002; de Hoon et al., 2003). Unaccounted for extraneous variables that may have plagued the study include the daily sodium intake of each
subject, the intake of food prior to testing, individual stress levels, medications, and the
time of day at which testing occurred.

The data show promise in the resulting trends for future studies. Through
examining the raw scores, the most significant finding was that blood pressure
measurements were all elevated in the experimental subject group as compared to the
age- and gender-matched control subject group. The extent of the elevation was about 10
mmHg for systolic pressure and about 5 mmHg for diastolic pressure. These elevations
are considered the upper limits of normal variation in blood pressure measurement. With
the trends in the age- and gender-matched data, it may be hypothesized that with a larger
subject pool the results will show statistical and clinical significance. However, this may
not be inferred from the current study. These results are in agreement with the body of
literature which suggests that migraines have larger autonomic responses than non-
migraines, as measured with blood pressure. This study has not shown agreement, but
may have with a larger subject pool, with previous studies reporting heart rate differences
between groups with migraines and without migraines. Blood-oxygen saturation levels
had not been examined in the literature at the time of this study. This investigation did
not yield any data that would suggest that this measure is sensitive enough to implicate
further examination.
CONCLUSIONS

The findings of this study result in the acceptance of the null hypothesis. No clinically significant between-group differences in physiologic responses were found as a result of vestibular and visual stimulation. Blood pressure trends in the age- and gender-matched group data appear to be promising, as a clinically significant finding, but need further investigation. Future research should include: an increased number of subjects, by using a multi-center approach or by extending the recruitment time; the addition of other subject populations, subjects with unilateral, bilateral, and central vestibular impairment; subjects with other headache types, as defined by IHS; symptomatic subjects; and subjects with migraines that are not regulated by medication use. Results and implications for clinical use in differentiating the MAD population from the non-MAD population could not be concluded from this study, but do show promise for future studies.
REFERENCES


APPENDIX A

This appendix includes all of the descriptive statistics for the group data comparisons and for the age- and gender-matched group comparisons. Each table represents one variable compared by group or age- and gender-matched groups. The first four tables define the statistics using group comparisons and the last four tables define the statistics using the age- and gender-matched comparisons.

Group Comparisons

Table A.

### Diastolic Pressure Descriptive Statistics for Group Comparisons

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<th>Std. Deviation</th>
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<td>Statistic</td>
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Table B.

### Descriptive Statistics for Group Comparisons of Systolic Pressure

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### Table C.

**Descriptive Statistics for Group Comparisons of Heart Rate**

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### Table D.

**Descriptive Statistics for Group Comparisons of Blood-Oxygen Saturation Levels**

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Descriptives for Matched-Paired Comparisons

Table E.

### Descriptive Statistics for Matched-Pair Groups of Diastolic Pressure

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Table F.

### Descriptive Statistics for Systolic Pressure of Matched-Pair Data

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<tr>
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<td>134</td>
<td>120.50</td>
<td>5.49</td>
</tr>
<tr>
<td>RC-VVOR</td>
<td>6</td>
<td>103</td>
<td>122</td>
<td>116.67</td>
<td>2.99</td>
</tr>
<tr>
<td>RC-OPK</td>
<td>6</td>
<td>109</td>
<td>136</td>
<td>122.33</td>
<td>4.22</td>
</tr>
<tr>
<td>Valid N (listwise)</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table G.

Descriptive Statistics for Heart Rate Comparisons of Matched-Paired Groups

<table>
<thead>
<tr>
<th>Post Test</th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>6</td>
<td>80.67</td>
<td>8.94</td>
<td>65</td>
<td>91</td>
</tr>
<tr>
<td>BaselineSOT</td>
<td>6</td>
<td>87.33</td>
<td>9.33</td>
<td>76</td>
<td>99</td>
</tr>
<tr>
<td>SOT1_3</td>
<td>6</td>
<td>89.00</td>
<td>10.81</td>
<td>72</td>
<td>98</td>
</tr>
<tr>
<td>SOT4_6</td>
<td>6</td>
<td>91.17</td>
<td>8.57</td>
<td>79</td>
<td>99</td>
</tr>
<tr>
<td>BaselineRC</td>
<td>6</td>
<td>88.33</td>
<td>6.53</td>
<td>80</td>
<td>98</td>
</tr>
<tr>
<td>VOR</td>
<td>6</td>
<td>89.17</td>
<td>8.04</td>
<td>77</td>
<td>98</td>
</tr>
<tr>
<td>VVOR</td>
<td>6</td>
<td>88.50</td>
<td>5.28</td>
<td>80</td>
<td>93</td>
</tr>
<tr>
<td>OPK</td>
<td>6</td>
<td>89.17</td>
<td>5.38</td>
<td>82</td>
<td>94</td>
</tr>
</tbody>
</table>

Table H.

Descriptive Statistics of Blood-Oxygen Saturation Levels for Matched-Pair Data

<table>
<thead>
<tr>
<th>Post Test</th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASELINE- 0</td>
<td>6</td>
<td>95</td>
<td>98</td>
<td>97.17</td>
<td>.48</td>
</tr>
<tr>
<td>Baseline- SOT</td>
<td>6</td>
<td>95</td>
<td>99</td>
<td>97.33</td>
<td>.62</td>
</tr>
<tr>
<td>SOT 1-3</td>
<td>6</td>
<td>96</td>
<td>98</td>
<td>97.17</td>
<td>.31</td>
</tr>
<tr>
<td>SOT 4-6</td>
<td>6</td>
<td>96</td>
<td>99</td>
<td>97.33</td>
<td>.49</td>
</tr>
<tr>
<td>Baseline- RC</td>
<td>6</td>
<td>94</td>
<td>98</td>
<td>96.33</td>
<td>.67</td>
</tr>
<tr>
<td>RC-VOR</td>
<td>6</td>
<td>95</td>
<td>98</td>
<td>96.67</td>
<td>.49</td>
</tr>
<tr>
<td>RC-VVOR</td>
<td>6</td>
<td>96</td>
<td>100</td>
<td>97.50</td>
<td>.56</td>
</tr>
<tr>
<td>RC-OPK</td>
<td>6</td>
<td>95</td>
<td>99</td>
<td>97.50</td>
<td>.56</td>
</tr>
</tbody>
</table>

Valid N (listwise) 6
APPENDIX B

This appendix displays all of the graphs that were not put into the paper. Figures 1. through 16. demonstrate the mean group comparison data and are separated by variables. The x-axis in each graph illustrates the post test interval at which measurements were obtained and the y-axis represents units of measurement for each variable.

Figures 17. through 24. show the age- and gender-matched pair data per subject set. Each subject set contains a control subject and an experimental subject. The x-axis defines the post test at which measurements were obtained and the y-axis depicts the units of measurement for each variable. One of the age- and gender-matched heart rate comparisons is also not included because it may be seen in the text of the paper on page 29.

![Mean Group Comparisons of Blood-Oxygen Saturation Levels](image)

*Figure 1. This graph displays the change in blood-oxygen saturation levels as the SOT testing progressed. No significance was found.*
Group Comparisons of Blood-Oxygen Saturation Levels

Control Group  Experimental Group

![Bar chart showing blood-oxygen saturation levels for control and experimental groups.]

Figure 2. This graph represents group comparisons of blood-oxygen saturation levels changes during Rotational Chair testing in both groups.

Mean Group Comparisons of Blood-Oxygen Saturation Level Fluctuations

Control Group  Experimental Group

![Line chart showing blood-oxygen saturation level fluctuations for control and experimental groups.]

Figure 3. This graph illustrates the amount of change in blood-oxygen levels between two test intervals during the sensory organization testing procedures. Interestingly, the experimental subject group has greater variability than the control group.
Figure 4. This graph depicts the change in blood-oxygen saturation levels between two test intervals for the rotary chair testing procedures. The experimental group appears to have greater variability in this graph as well as in the fluctuations of the SOT procedure.

Figure 5. This chart illustrates diastolic pressure measurements at each SOT post test interval. The asterisk denotes statistical significance at $p<0.05$. 

49
Figure 6. This graph shows the post test interval during rotational chair testing (VOR) at which the diastolic pressure of the experimental group was significantly greater than that of the control group. This graph also demonstrates increased variability in the experimental group.

Figure 7. This graph depicts the change in the diastolic pressure between two test intervals for computerized dynamic posturography testing procedures. The experimental group appears to have greater variability and fluctuation during the SOT procedure.
Mean Group Comparisons of Diastolic Blood Pressure Fluctuations

Control Group

Experimental Group

Diastolic Pressure in mmHg

Post Test

Figure 8. This figure represents the change in the diastolic pressure between two test intervals for rotational chair (RC) testing procedures. The experimental group appears to have greater variability and amounts of fluctuation in the RC procedures.

Mean Group Comparisons for Systolic Pressure

Control Group

Experimental Group

Systolic Pressure in mmHg

Post Test

Figure 9. This figure displays the group mean comparison of systolic pressure in relation to stimulation utilizing the SOT. Significant findings were present in the measurements obtained after the third condition of the SOT and are denoted by the asterisk.
Figure 10. Group mean comparisons of systolic pressure, as measured during rotary chair testing, are depicted in this graph. The experimental group shows more variability than the control group.
Figure 11. The amount of systolic pressure change between testing intervals is shown with this figure. Increased variability is seen in the experimental group and increased fluctuations is seen in both groups.

Figure 12. The amount of systolic pressure change between testing intervals is shown with this figure. Increased variability and fluctuations is seen in the experimental group as compared to the control group utilizing the rotary chair procedures.
Figure 13. This figure represents the between-group comparison of heart rate during SOT testing in both groups.

Figure 14. Mean group heart rate comparisons are illustrated on this graph. These measurements were obtained after each test procedure.
Figure 15. This graph depicts the change in the heart rate between test intervals for computerized dynamic posturography testing procedures. The experimental group shows greater variability during the SOT procedures.

Figure 16. This figure depicts the change in the heart rate between test intervals for rotary chair testing procedures. The experimental group has much greater variability during these procedures.
Age- and gender-matched comparisons for individual subject sets.

Figure 17. This figure is a comparison of heart rate for two matched subjects across the span of testing.

Figure 18. This is another age- and gender-matched paired heart rate comparison. This comparison shows fluctuations in both subjects.
Figure 19. This is a depiction of two of the matched-pair subjects comparison of diastolic pressure over all test intervals.

Figure 20. This figure is a comparison of two matched-pair subjects systolic pressure over all test procedures.
Figure 21. This displays another set of matched-paired subject data and compares the diastolic pressure over testing intervals.

Figure 22. This graph displays the contrast between systolic pressure measurements for two matched subjects throughout testing procedures. The general trend is increased systolic in the experimental subject versus the control subject.
Figure 23. This figure illustrates the trend of the diastolic pressure to be generally increased in the experimental subject population as compared to their matched counterpart.

Figure 24. This graph shows the general trend of increased systolic pressure in the experimental subjects as compared to the matched-control subject.