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ABSTRACT

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Objective: Osteopathic Manipulative Medicine treatment (OMT) regimes often focus on treating the Autonomic Nervous System (ANS) in addition to biomechanics. Techniques focused on the upper cervical spine are theorized to affect the function of the vagus nerve and thereby influence the parasympathetic branch of the ANS. This study was conducted to observe the effect of upper cervical spine manipulation on cardiac autonomic control as measured by heart rate variability (HRV).

Methods: Nineteen healthy, young adult subjects were randomly assigned an order in which they would undergo three different experimental protocols: OMT, Sham, and a time control. Six minutes of electrocardiographic data was collected before and after each intervention to be analyzed by power spectral analysis.

Results: All baseline data for each protocol and all parameters studied were the same. The OMT protocol caused a change in the standard deviation of the normal-to-normal (SDNN) intervals (0.121 +/- 0.0822 sec, p=0.005) and the change in the high frequency HRV was different from the changes caused by the other interventions (p=0.038).

Conclusions: This preliminary data supports the hypothesis that upper cervical spine manipulation affects the parasympathetic nervous system; however, more data on more subjects needs to be collected in order to clarify some points, and to reach statistical significance in certain measures.

EFFECTS OF CERVICAL MANIPULATION ON CARDIAC AUTONOMIC CONTROL

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CHAPTER 1

BACKGROUND AND SIGNIFICANCE

INTRODUCTION TO OSTEOPATHY

Osteopathic medicine is a form of health care defined by the application of its philosophy. Andrew Taylor Still, a practicing physician of the late nineteenth century, grew frustrated with the inadequacies of the contemporary medicine of his time and sought to develop a new way of approaching the practice of medicine (*Foundations for osteopathic medicine*2003). From this grew the osteopathic philosophy of medicine, based on the following four principals:

1) The Human being is a dynamic unit of function.
2) The body possesses self-regulatory mechanisms that are self-healing in nature.
3) Structure and Function are interrelated at all levels.
4) Rational treatment is based on these principles (W. Kuchera, W., D.O. & Kuchera, 1994)(*Foundations for osteopathic medicine*2003).

These principles not only reflect his belief that man was constructed by God; but, by understanding that construction, a physician would better be able to assist the body in its natural ability to maintain health (*Foundations for osteopathic medicine*2003). This led to the extensive study of anatomy. Anatomy, a structural science, is easily related to the functioning of the body as a whole. The structure and function of bones, joints, vessels, muscles, organs, and nerves did not stop the understanding of each in isolation; but continued into the varied ways in which one structure can affect a multitude of others through direct connection or a chain of connections (*Foundations for osteopathic medicine*2003). These changes to structure or position and how they can affect function can be observed on the gross scale in the example of a broken leg (altered structure), or a dislocated shoulder (altered position). On the smaller scale, constricting a vessel restricts its ability to deliver nutrients or remove wastes.

Through the study of anatomy, and the use of the four principals, A.T. Still incorporated an extensive form of physical diagnosis and medical treatment in addition to his contemporary knowledge of medical practices at the time. The use of this specific form of physical diagnosis and manual therapy has often been pointed to as being the differentiating factor between osteopathic physicians and allopathic physicians, because it is the one formal aspect of the curriculum that all schools of osteopathic medicine teach in addition to the standard allopathic coursework. While this Osteopathic Manipulative Medicine (OMM) is a direct result of the aforementioned principles, it is the principles by which osteopathic physicians choose to define themselves.

These somewhat simple principles, developed through the study of anatomy, have continued to show application to each new science as it develops, from physiology, to microbiology, pharmacology, biochemistry, and potentially to molecular biology and proteomics. Nevertheless, the scientific proof of effect and mechanism of action for many of the osteopathic principles remains to be determined. Thus, the focus of this research was one small step in the determination of the physiological consequences of a specific cervical manipulation technique in which traction is placed on the occiput. Details of the anatomy of the upper cervical spine are described below, particularly as it applies to the manipulation in the region of the occiput.

ANATOMY OF THE UPPER CERVICAL SPINE

At the top of the cervical spine is the occipital bone (*Gray's anatomy*1989). This bone articulates directly with the parietal bones, temporal bones, sphenoid, and the first cervical vertebra (*Gray's anatomy*1989). Of importance to this study is the jugular foramen, located between the occipital bone and the temporal bone (*Gray's anatomy*1989). Note in jugular foramen within the double circle on anatomy plate 1(*Gray's anatomy*1989). The vagus nerve passes through this foramen and its function will be discussed in greater detail later (*Gray's anatomy*1989). Through attachment with more than ten different muscles, the occiput also connects to the vertebrae from C1 to T12, the scapula, the clavicle and the sternum (Anatomy Plate 2) (*Gray's anatomy*1989). Anatomy plate 2 shows various locations muscles attach to the skull, notice the large number attaching to the occiput as well as two that cross the occipito-temporal suture (*Gray's anatomy* 1989). These muscles provide much of the gross range of motion for the head and neck (*Gray's anatomy*1989). Many osteopathic manipulative medicine techniques exist to affect these structures directly or indirectly by means of these anatomic interconnections – the effect to one structure can be carried over to another through muscular, ligamentous, or fascial connection Note the large number of anatomical structures, in multiple layers, depicted in Anatomy slide 3 (Netter 1987).

The first cervical vertebrae is below the occiput, named the atlas, and together they form the atlanto-occipital joint (*Gray's anatomy*1989). The atlas is an atypical cervical vertebra for not having a vertebral body or transverse processes (*Gray's anatomy*1989). The occipital condyles articulate with the two superior articular surfaces of the atlas (*Gray's anatomy*1989). The predominant motion allowed by the atlanto-ooccipital joint is in the sagital plane providing for flexion and extension (*Gray's anatomy*1989). The recti capitis posteriores major and minor attach at the occiput and the atlas and are involved with extension of this joint (*Gray's anatomy*1989). There is also some lateral flexion (side bending) that occurs at this joint (*Gray's anatomy*1989). The atlas on the second vertebrae, named the axis, forms the atlanto-axial joint (*Gray's anatomy*1989). The axis is another atypical cervical vertebrae having a dens projecting superiorly from its body and articulating with the anterior arch of the axis (*Gray's anatomy*1989). The cruciate ligaments, the alar ligaments, and the tectorial membrane reinforce this particular articulation (*Gray's anatomy*1989). The unique conformation of the atlanto-axial joint allows for a pure rotational range of motion (*Gray's anatomy*1989). The obliqui capitis superior and inferior attach to the atlas and the axis and are involved in the rotation of this joint

(*Gray's anatomy*1989). The remaining bones of the cervical spine, vertebrae three through seven, are similar in structure and function. The vertebral bodies and intervertebral disks bear much of the weight in a neutral position, with the articular surfaces of the articular pillars restricting the flexion, extension, rotation, and side bending at each joint. The Longus capitis, longus colli, scalenes, rotatres cervicis, interspinalis cervicis, and the trapezius muscles all attach to the typical cervical spine (*Gray's anatomy*1989). All of these structures are known to play a role in the determining the range of motion of the neck. As a consequence, a muscle spasm in one fiber, or altered position of a specific bone, can change the overall function of the neck by reducing the range of motion. In addition, it is theorized that such an alteration in position not only reduces the motion of the structures; but, it puts a facial stress on the nerves and vasculature in the area and thereby reduces their overall ability to respond appropriately to stimuli. Conditions in which there is altered function associated with impaired motion is an important target of osteopathic manipulative treatment in the cervical spine.

The anatomical relationship of the efferent vagus nerves to the musculoskeletal arrangement at the occiput described above lends credence to the hypothesis that OMT at this location could affect vagal functions. The vagus originates for several rootlets located in the medulla oblongata (*Gray's anatomy*1989). These rootlets form a flat cord before exiting through the jugular foramen (formed between the temporal and occipital bones)(*Gray's anatomy*1989). The initial path out of the skull accompanies the accessory nerve sharing a common arachnoid and dural sheath (*Gray's anatomy* 1989). Continuing its descent in the carotid sheath, the right and left vagus take a differing course once they pass the common carotid artery at the root of the neck (*Gray's anatomy* 1989). Despite these differences from one side to another, both nerves descend through the superior mediastinum and branch to innervate the lungs once past the hilum (*Gray's anatomy* 1989). A few of these branches reunite to form the anterior and posterior esophageal plexuses from the left and right vagus, respectively (*Gray's anatomy* 1989).

The cardiac plexus is divided into a superficial (ventral) and deep (dorsal) section (*Gray's anatomy* 1989). The superficial part of the cardiac plexus receives its vagal contribution from the left vagus, originating from lower two cervical cardiac branches (*Gray's anatomy* 1989). The deep cardiac plexus receives vagal innervations from both sides with the additional branches exiting from the right vagus near the trachea (*Gray's anatomy* 1989). The cardiac efferent fibers of the vagus nerve originate near the nucleus ambiguous (*Gray's anatomy* 1989). The intrinsic innervations are limited primarily to the atria and septum of the heart, being most abundant in the subepicardial connective tissue near the sinoatrial and atrioventricular nodes (*Gray's anatomy* 1989). Innervation of the ventricular myocardium is sparse, but nevertheless may be of clinical significance due to effects on the cardiac conduction system (*Gray's anatomy* 1989).

The anterior esophageal plexuses from the left vagus then combine to enter the abdomen as the anterior vagal trunk (*Gray's anatomy* 1989). The right vagal plexus travels in parallel with the left vagus and enters the abdomen as the posterior vagal trunk (*Gray's anatomy*1989). The anterior vagal trunk supplies the stomach whereas the posterior vagal trunk innervates the spleen, liver, kidneys, adrenal glands, a small portion of the stomach, and the mesenteric plexuses (*Gray's anatomy*1989).

AUTONOMIC NERVOUS SYSTEM

In terms of physiological function, the autonomic nervous system (ANS) is responsible for the majority of involuntary neurological control of the body (Willard, 2003). This system is divided into two sides based on their function – the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) (Willard, 2003).

The sympathetic nervous system has been called the thoracolumbar division of the ANS because its nervous supply exits the central nervous system from the spinal cord at the levels of the thoracic and lumbar spine (*Medical physiology*1995). By coordination with the hypothalamus, the many branches of the SNS are often able to fire simultaneously in response to stress (exercise, emotional, perceived danger, etc.) (*Medical physiology*1995). These collective responses are commonly referred to as the 'fight-or-flight' response (*Medical physiology*1995). In general, most of the physiological effects are excitatory in nature, resulting in increases in metabolism, smooth muscle tone and electrical and contractile activity within the heart.

The parasympathetic nervous system finds it origins in the brain stem and the sacral plexus, and has thus been referred to as the craniosacral division of the ANS

(*Medical physiology*1995). In general, stimulation by the PNS often produces effects that are reciprocal to the effects caused by SNS stimulation (*Medical physiology*1995). To this end, the PNS is commonly known to govern the 'rest-and-digest' functions of involuntary neurological control (*Medical physiology*1995).

Both sides of the ANS innervate most organs (with the exception of skin, skeletal muscle, and most blood vessels); and thereby, play reciprocal roles in most visceral functions. This also results in autonomic control being in a state of constant change such that the *balance* between the two branches also varies as to which side predominates at any given moment (Willard, 2003). As opposed to the motor end plate formation found in skeletal muscle, the postganglionic fibers of the ANS end in swellings rich in synaptic vesicles (*Medical physiology*1995). The neurotransmitters are released into the extracellular space near effector cells and affect the appropriate receptors at the end-organ tissue (*Medical physiology*1995). Thus, the differentiation of each side lies in the postganglionic neurotransmitter used and the receptor stimulated (*Medical physiology*1995). The PNS uses acetylcholine (Ach) while the SNS uses norepinephrine (NE) as the respective neurotransmitter (*Medical physiology*1995).

In the heart, the vagus nerve supplies the parasympathetic innervations while the sympathetic fibers leave from the T1-T4 spinal levels (*Medical physiology*1995). The vagus nerve releases acetylcholine to interact with the muscarinic receptors in the sinoatrial node, the atrioventricular node, and some specialized conducting tissues (*Medical physiology*1995). This stimulation leads to a decrease in the heart rate and the conduction velocity through the heart (*Medical physiology*1995). The SNS releases norepinephrine which binds to beta-1 adrenergic receptors of the sinoatrial node, the atrioventricular node, the conducting tissue, and the myocardium of the atria and ventricles (*Medical physiology*1995). Sympathetic stimulation normally increases heart rate, conduction velocity and contractility within both the atria and ventricles (*Medical physiology*1995). The constant interplay between the SNS and PNS results in a rhythmic fluctuation as to which side of the ANS dominates in controlling heart rate at any given moment. Under quiet conditions in a healthy individual the parasympathetic nervous system dominates these heart rate variations; however, when the system becomes stressed this balance between the parasympathetic and sympathetic influences on the heart shift progressively to a more sympathetic-dominated state.

Analysis of the rhythms of heart rate variations over time has been shown to provide insight into how the ANS is modulating the heart (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). In its resting state, the parasympathetic tone prevails and variations in heart period depend mostly on vagal modulation as noted above, and these variations appear to be coordinated with respiration which creates fluctuations at the frequency of respiration ((Levy, 1971)(Chess, Tam, & Calaresu FR, 1985)). This rhythmic interplay between the two sides of the ANS is of interest to osteopathic physicians because, as described below, they are interested in assisting the body to reach its optimal level of function and often do so by trying to affect one side of the

ANS to restarts the inherent mechanism of checks and balances that may be disturbed by a pathologic process. Before this theory of osteopathic manipulative medicine can be fully tested, it is important to first determine whether or not, and how, specific manipulative interventions can affect the ANS and end-organ effects of those changes. The variations in heart rate described above are a quantitative tool that can be used to achieve this goal. Details of the analysis of these rhythms is described in more detail below.

OSTEOPATHIC MANIPULATIVE MEDICINE (OMM)

The use of the previously mentioned osteopathic manipulative medicine (OMM) is directed at areas of the body termed somatic dysfunction. Somatic dysfunction is defined as the impaired or altered function of related components of the somatic (body framework) system: skeletal, arthrodial, and myofascial structures, and related vascular, lymphatic, and neural elements (*Foundations for Osteopathic Medicine,* 2003). When considering the use of OMM in a visceral disease process, osteopaths address the sympathetic innervations, the parasympathetic innervations, and the lymphatic drainage (Kuchera & Kuchera, 1994).

In the case of sympathetic innervation, osteopaths may choose to use a technique termed 'rib-raising' to affect the SNS (*Foundations for Osteopathic Medicine,* 2003). As alluded to earlier, the sympathetic fibers exit the spinal cord at the level of the thoracic and lumbar spine (Willard, 2003). These fibers synapse into the sympathetic chain ganglia lying on the lateral vertebral bodies (Willard, 2003). In the case of the thoracic spine, the sympathetic chain ganglia are also found in close association with where the ribs articulate on the vertebral body (Willard, 2003). Therefore, in order to affect the sympathetic half of the autonomic control to a visceral organ, an osteopath will take advantage of this close anatomical proximity by making use of 'rib-raising (Kuchera & Kuchera, 1994).' In this technique, the patient is lying on their back and the osteopathic physician contacts the patient's skin overlying the angles of the ribs (*Foundations for Osteopathic Medicine,* 2003). Following this, an anterior pressure is applied to each rib angle, and in turn translated to the rib heads (*Foundations for Osteopathic Medicine,* 2003). This motion of the rib head, in close proximity to the sympathetic chain ganglia, is the theorized way in which osteopaths affect the SNS.

Regarding the PNS, osteopaths seek to alter its current state by stimulating the nerves involved (Kuchera & Kuchera, 1994)(*Foundations for Osteopathic Medicine,* 2003). This requires the osteopath to focus on the cranial and sacral areas of the patient. The vagus nerve supplies parasympathetic innervations to many visceral organs in the body, and as a result, many techniques have been developed in an attempt to affect the state of the vagus nerve. The specific technique I chose to investigate in this study is the sub-occipital decompression. This technique focuses on somatic dysfunction found at the base of the skull; and by removing it; the tortuous pathway of the vagus out of the skull and down the neck may be free of structural stresses. A possible example would be a spasm of the sternocleidomastoid. A tight, constant pull on the left side of the occiput could reduce the normal motion found at the left occipito-temporal suture and reduce the size of the left jugular foramen. This situation may not result in osseous nerve impingement; however, it is theorized to alter the functional firing of the vagus nerve. While an osteopath would not claim to know if this situation results in increased or decreased firing, they would state this condition limits the nerves ability to respond adequately to stimuli by being in a constant state too far to one side of homeostatic equality.

The autonomic nervous system is in constant ebb and flow (*Medical Physiology,* 1995). Some disease states can be characterized by an increased sympathetic activity or an increased parasympathetic activity (Kuchera & Kuchera, 1994). However, osteopaths do not claim their techniques can push the ANS to one side or the other. Osteopaths try to assist the body in regaining its own self-regulatory mechanisms (W. Kuchera, W., D.O. & Kuchera, 1994). In disease states in which the SNS is predominating to a detrimental degree, an osteopath would stimulate both sides of the ANS – not to force shifting one direction or the other, but simply to introduce a new imbalance in the pathologic state of the ANS and allow the self-regulating mechanisms inherent to the ANS to reset the balance to a more physiologic state. Nevertheless, under most conditions the most "normal" state of health is a condition in which there is high vagal activity and control and relatively low sympathetic activity and control.

HEART RATE VARIABILITY (HRV)

It is well known that a person's heart rate increases in response to cardiac need, such as exercise, fright, or in clinical conditions. Moreover, over time in synchrony with respiration and other rhythms within the body the precise amount of time between consecutive heartbeats tends to fluctuate resulting in a heart rate that varies on a beat-to-beat basis. In general, this beat-to-beat or moment-to-moment variation of heart rate is referred to as heart rate variability.

Clinical appreciation of this phenomenon was first reached in 1965 by Hon and Lee when they noted fetal distress was preceded by alterations in interbeat intervals before a change in overall heart rate was noticeable (Hon & Lee, 1965). Wolf et al. found an overall decrease in the variation of the beat-to-beat interval to be associated with a higher risk of post-infarction mortality in 1977 (Wolf, Varigos, Hunt, & Sloman, 1978). Further quantitative assessment of HRV was introduced by Akselrod et al. in 1981 by the addition of power spectral analysis (Akselrod et al., 1981). The result of these ground-breaking studies was that there were two general approaches to assessing heart rate variability that appeared to be related, and most importantly there appeared to be some potential clinical significance to the measurement of HRV. In general, there are two classifications of the analysis of HRV: Time domain and frequency domain. I used measurements of both types in this study and details of some of the techniques and interpretation of these measures are described below.

HRV in the Time Domain

One method in which to analyze HRV is found within the time domain. In a continuous electrocardiographic (ECG) tracing, the normal-to-normal (NN) interval is measured between adjacent QRS complexes resulting from a normal, sinus node depolarization (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Another term found in various articles concerning HRV is the R-R interval, or the time between adjacent R-waves on the tracing. I will use the NN terminology because I believe it more precisely describes the unit of time measured, the time between normal heart beats, not between any set of R-waves. The longer the time period, over which the data is collected, the more complex the statistical time-domain measure is to calculate (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The analysis is performed directly on the NN intervals, or on the derived values from the differences between NN intervals (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

The simplest calculation of HRV in the time domain is the standard deviation of the NN intervals (SDNN)(Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). SDNN is commonly calculated over a 24 hour period to include both the high and low frequency variations which normally occur and which can be quantified in the frequency-domain as described below (Task Force of the European Society of

Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The total statistical variance detected with this method of analysis increases with the length of analyzed recording; therefore, comparing ECG tracings of differing lengths would not be appropriate (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The two most common lengths of recording reported by the joint task force on HRV are five minuets and 24 hours (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The SNDD in shorter timeframes (5 minutes or less) is more sensitive to vagal control effects, but also reflects some sympathetic modulation of heart rate (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). A limitation of this technique is that it is greatly affected by large abrupt changes in heart rate that may reflect only a very transient shift in autonomic tone (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). An example of this would be expected with an abrupt change in body position transitioning from supine to standing or with progressive increases in exercise intensity which would result in progressive increases in heart rate. Those increases in heart rate *per se* will cause an increase in the HRV which does *not* reflect the modulation of heart rate by the ANS. Thus, it is important to recognize that HRV reflects the *control* of heart rate by the ANS, and not simply the activity of the ANS.

Other statistical measures of the time domain include: standard deviation of the average NN (SDANN) – calculated from five minute periods over a 24 hours strip; the square root of the mean squared differences of successive NN (RMSSD), the number of interval differences of successive NN intervals great than 50ms (NN50), and the proportion derived by dividing the NN50 by the total number of NN intervals (pNN50) (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Each of these measures tends to correlate closely with SNDD and was not used in this study.

<u>HRV in the Frequency Domain</u>

Application of a power spectral analysis by using a Fast Fourier Transform (FFT), one is able to study the frequencies at which heart rate varies (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Very Low Frequency (VLF), Low Frequency (LF), and high frequency (HF) are the main spectral components measurable from a short term tracing of five minutes (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). However, the value of the VLF obtained from ECG tracing of five minutes is not related to normal autonomic modulation and will not be evaluated in this study (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). In long term recordings, an additional Ultra Low Frequency (ULF) can be discerned; but even less is known about the significance of this frequency oscillation (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Below, I describe the primary quantitative elements of a spectral analysis of heart rate. These include the high frequency and low frequency bands.

High Frequency: The range for the high frequency heart rate variation is 0.15 to 0.4 Hz (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The high frequency variation has been shown to be associated with respiration as it occurs at the respiratory frequency. It is produced purely by the vagal output because complete muscarinic blockade with atropine results in loss of HF variation in this frequency range (Pomeranz et al., 1985). This frequency of variation is also missing in individuals after either vagotomy or heart transplant surgery (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). In both cases, there is no vagal modulation of heart rate. Thus, collectively, these findings show that the HF range of HRV is a quantification of vagal control of heart rate.

Low Frequency: The low frequency variation ranges from 0.04 to 0.15 Hz (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Comparing the amount of total HRV in a healthy subject in the supine position, and then in the standing position, one finds little change in the overall variation; however, the relative amount of LF variation increases from lying to stand, while HF decreases (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The use of atropine to block muscarinic receptors reduces the amount of low frequency variation, but not to the extent that it does for the high frequency range of HRV (Pomeranz et al., 1985). So while the vagus nerve may contribute to the low frequency variation, it is not the only contributor; and thus, this measure is more complicated (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Cardiac sympathetic blockade (with a beta-1 adrenergic blocker) also reduces the LF spectral power, thereby suggesting that LF is in part mediated by the SNS. Thus, the LF range of HRV is described as a balance between the SNS and PNS influences on heart rate.

The Ratio of Low Frequency to High Frequency: Because the HF variation is known to be parasympathetically-mediated, and the LF variation is mediated to only some degree by the PNS, it is theorized that the remainder of the influence is brought about by the SNS (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). For this reason, the value of high frequency change can be divided out of the low frequency change to provide a possible measure of sympathetic control of heart rate (Task Force of the European Society of Cardiology and the North American Society of Pacing and

Electrophysiology, 1996). This ratio is sometimes estimated in an attempt to "quantify" the sympathetic control of heart rate. This too is problematic as a reliable interpretation of changes in sympathetic control. In part, this is confounded by the fact that systematic changes in the high frequency spectral power are not associated with either parallel or reciprocal changes in the low frequency power; thus, it is difficult to predict from changes in both how the change in vagal control has affected the power in the LF frequency.

Clinical Implications of Heart Rate Variability

Clinically, lower HRV has been correlated with a variety of pathologic states, from diabetic neuropathy and myocardial infarction (Pumprla & et. al, 2002)(Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) to clinical depression (Nahshoni & et. al., 2004) and higher levels of perceived stress (Dishman & et. al., 2000). Patients with essential hypertension have detectable changes in HRV and associated increase in SNS activity. Control of hypertension is associated with an increase in the HRV in addition to a decrease in cardiovascular morbidity and mortality (Pumprla & et. al, 2002). This decrease in HRV has therefore been used as an indicator of abnormal and insufficient adaptability of the ANS (Pumprla & et. al, 2002). Recent studies have shown that HRV is prognostically predictive of sudden death after myocardial infarction (La Rovere, 2000). This brief synopsis of clinical implications of HRV only scratches the surface of the literature in which HRV appears to provide some insight into health, risk of disease and/or associated autonomic dysfunction.

Although HRV has limitations to its utility and physiological meaning, its application has clearly been shown to be clinical worthy in many cases. The value of HRV in clinical application continues to be refined, but it also continues to be a valuable tool to assess conditions or therapies in which changes in ANS function are achieved. The application to osteopathic manipulative medicine is potentially an important research area in which it appears to be useful. Heart rate variability provides an index of ANS function in which a non-invasive measure is obtained and which can be assessed while manipulation is applied: this is uniquely attractive for the study of manual therapies and allowed the development of the following specific aim.

SPECIFIC AIM

OMT of the cervical spine, particularly as it influences the structures associated with the occiput are theorized to affect the PNS. Therefore, the specific aim is to determine the effects of OMM to the cervical spine on short-term vagal control of heart rate by assessing HRV.

HYPOTHESIS

I hypothesize that OMM will increase Heart Rate Variability measures of vagal control when compared to sham and time control protocols.

CHAPTER 2

METHODS

INTRODUCTION

To study the changes brought about in Heart Rate Variability (HRV) by Osteopathic Manipulative Medicine (OMM) a series of three protocols were designed to control for possible confounding variables. The osteopathic manipulative techniques chosen (soft tissue, and sub-occipital decompression), the sham protocol and the time control will all be explained in further detail below. A crossover design was chosen to minimize subject variation effect and to maximize the power provided by a small sample size in this pilot study.

SUBJECT SELECTION

The study population of 24 healthy subjects was selected from a narrow age group – 18 to 35 years of age – in order to have a homogeneous group of subjects. Because this study will also depend on the normal function of the autonomic nervous system (ANS), the following exclusion criteria were also established:

- Consumption of caffeine within the past 4 hours
- Use of tobacco within the past 48 hours
- Use of illegal drugs within the past week
- History of cardiovascular disease

- History of neuropathic disorders
- Unexplained episodes of syncope

Recruitment for these subjects was performed on the University of North Texas Health Science Center campus. Recruitment methods included campus wide e-mail and posting of flyers in public spaces. Participation in the study was completely voluntary. Each subject provided signed written consent before participation in any aspect of the study.

STUDY DESIGN

Upon entrance into the study, each subject was randomly assigned an order in which they underwent the Osteopathic Manipulative Treatment (OMT), sham, and time control protocols, each serving as their own control. Upon arriving to the laboratory, the subject was explained the basics of the protocol without indicating any specifics of the OMT or sham treatments. The subjects were then instrumented with patch electrodes for the measurement of a standard limb lead electrocardiogram.

Each protocol started with a 20-minute period of quiet, supine rest to allow the subjects' autonomic nervous system to reach base line. Prior to the OMT and sham interventions, six minutes of an electrocardiography (ECG) rhythm strip was obtained. Immediately following the completion of the OMT or the sham protocol, an additional 6 minutes of an ECG rhythm strip was collected. For the time control protocol, a 15-minute ECG rhythm strip was collected following the twenty-minute period of quiet supine rest. From this, a six-minute segment was chosen immediately after the twenty-minute preparatory rest and again during the last 6 minutes of the time control segment to mirror the data collection time periods set forth in the OMT and sham protocols. Six minutes of ECG was chosen to allow for analysis of the HRV in both the time and the frequency domains (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

After completion of the first protocol, each subject ambulated for five to ten minutes before starting with the twenty minutes of quiet, supine rest for the next protocol. This period of ambulation was repeated between the second and third protocols as well. Subjects were allowed to void if necessary. Figure 1 shows a schematic representation of the study design.

INTERVENTIONS

The three interventions that each subject completed in this study were: 1) an OMT intervention, 2) a Sham or placebo intervention, and 3) no intervention, or a time control.

OMT

The OMT protocol involved the preparation of the subject's posterior cervical musculature by using the two soft tissue techniques of kneading and stretching. Kneading is a process by which a force is applied perpendicular to the long axis of the muscle (OPP). Stretching is accomplished by separating the origin and insertion of a muscle (OPP). Following this, the treatment provider performed the following procedure for a sub-occipital decompression (adapted from the Kimberly Manual) (Kimberly, 2000):

The subject laid supine and the study treatment provider sat at the head of the table. The study treatment provider used their index fingers to contact the occiput as near to the occipital condyles as possible. The index fingers were reinforced with the middle fingers. Tension was then applied toward the orbits to make firm contact with the occiput. The study treatment provider applied traction while their elbows were moved medially. The study treatment provider made minor adjustments in all three planes of motion, as needed, to maintain ligamentous balance. The study treatment provider held the point of ligamentous balance until the best motion in the joint was obtained (Kimberly, 2000).

Sham Treatment

This procedure was included in the study in attempt to control for any effect that human contact may have on the autonomic nervous system or the Heart Rate Variability (HRV) of the subject. The sham protocol was adapted from the OMT protocol. The two soft tissue techniques were not used prior to the sham protocol. Fingers were placed near the occipital condyles; however, no tension was applied in any direction, the subject's head was simply held in the treatment provider's hands for one minute. The pressure used on the subjects head and neck did not exceed 5 grams.

Time Control Condition

The time control protocol is simply a no intervention protocol. The protocol was included to control for the effect lying supine for fifteen minutes has on HRV.

DATA COLLECTION AND ANALYSIS

In addition to repeated six-minute electrocardiographic rhythm strips during the different intervention periods, each subject's age, gender, body mass index, and self-reported physical fitness level (number of hours of regular exercise per week) were recorded for comparison of possible confounding factors.

All physiologic data were recorded digitally on computer using a customized data acquisition system (WINDAQ, Akron, OH). All analyses were performed *post hoc* using the software and techniques described below.

Frequency-domain Analyses

Power spectral analysis was used to estimate autonomic control of heart rate. From each data set, a six-minute period of beat-to-beat pulse interval (RRI), were analyzed for time-domain measures including the mean heart rate and RRI and the standard deviation of normal-to-normal heart beats (SDNN). This time series was then converted into the frequency domain by fast Fourier transformation using commercially available software (DADiSP/AdvDSP, Cambridge, MA). Specifically, the spectral analysis was performed as follows. After resampling, the data were detrended with a third order polynomial fit, Hanning filtered and divided into 128 point segments with 50% overlap for fast Fourier transform (Welch method) (Marple, S. J., 1987). using data analysis and display software (DSP Development Corporation, Cambridge, MA). Harmonic LF (0.04-0.15 Hz) and HF (0.15-0.30 Hz) power was be extracted (Querry, R., et al. (1998), Raven, P. B., et al. (1998), Wang, H., et al. (1997), Wray, D. (1999), Wray, D., et. al. (2001)). High Frequency HR variability before and after normalization, HF_{nu} = HF/(LF+HF), was be applied as an index of vagal-cardiac modulation.

Statistical Analyses

All data sets were initially tested for normality using a Shapiro-Wilk statistic. For all normally distributed data, parametric statistics were used, whereas, for data sets that failed the normality test, non-parametric analyses were performed. Initially, the pre-treatment baseline data for each treatment condition were compared using a one-way analysis of variance. Since these data were equivalent for all variables, pairwise comparisons were used for all other analyses: paired T-test when the data were normally distributed, or Wilcox on signed rank test when the data were not normally distributed. For all analyses, significance was set an alpha level of 0.05. All data are reported as mean +/- SEM.

CHAPTER 3

RESULTS

INTRODUCTION

A total of 24 subjects were enrolled into this study. Three were unable to complete the study, and an additional two subjects were missing parts of the data set, and were therefore removed from the analysis. The result was a total of 19 subjects providing 57 data sets for analysis

DEMOGRAPHICS OF STUDY POPULATION

A total of 19 subjects were used in the analysis of this study. Of these subjects, six were male and thirteen were female. The average age of the subjects was 25 years with the median being 25 years, a minimum of 22 years, and a maximum of 31 years. The average body max index for the study was 23 kg/m^2 with a median of 21 kg/m^2, minimum of 18.56 kg/m^2 and a maximum of 29.82 kg/m^2. Eighteen of the nineteen subjects were Caucasian and one subject was Asian. See Table 1 for a more detailed view of demographics.

HRV DATA

The baseline data collected at rest for each subject before each intervention were analyzed using a one way repeated measures analysis of variance and baseline values f or all variables were found not to be significantly different, $p > 0.076$ (see Figure 2).

Change Due To An Intervention

Time Domain

The one time domain parameter analyzed in this study was the standard deviation of NN intervals, the SDNN. The Osteopathic Manipulative Treatment (OMT) intervention showed a statistically significant increase in the SDNN of 0.121 +/- 0.0822 sec from 0.151 +/- 0.0503 sec to 0.272 +/- 0.0694 sec with a p=0.005 (figure 3). The change in SDNN after the sham [0.0116 +/- 0.0648 sec; p=0.922] and time control [0.157 +/- 0.0756 sec; p=0.113] protocols was found to be not statistically significant (Figure 3).

Frequency Domain

In the frequency domain, the change in low frequency (LF), high frequency (HF) and the ratio of low frequency to high frequency (LF/HF) were evaluated using a paired t-test.

Low Frequency (LF): OMT, sham, and time control were not found to produce a statistically significant difference. OMT produced a change of -0.0000141 +/- 0.0000894 Hz; p=0.876. Sham produced a change of 0.0000456 +/- 0.000147 Hz;

p=0.761. The time control produced a change of 0.000232 +/- 0.000178 Hz; p=0.145 (Figure 4).

High Frequency (HF): OMT, sham, and time control were not found to produce a statistically significant difference on HF. OMT produced a change of 0.000167 +/- 0.0000869 Hz;p=0.071. Sham produced a change of 0.000115 +/- 0.000126 Hz; p=0.374. The time control produced a change of 0.0000565 +/- 0.000109 Hz; p=0.611 (Figure 5). However, when the change in HF was compared among interventions, significant differences were observed (see below).

Ratio of Low Frequency to High Frequency (LF/HF): The change in LF/HF due to the time control protocol was found to statistically significant, changing from 1.262 +/- 0.344 to 1.926 +/- 0.545 for a total change of 0.664 +/- 0.418; p=0.018; while OMT and Sham were not statistically significant. OMT produced a change of -0.791 +/- 0.659; p=0.293. Sham produced a change of 0.290 +/- 0.214; p=0.332 (Figure 6).

Comparisons Between Interventions

Time Domain

When comparing the effects of each intervention to each other in the time domain, there was no comparison found to be significantly different. The change in SDNN caused by OMT (0.121 +/- 0.082 Hz) was not significantly different from either the time control (0.157 +/- 0.076 Hz, p=0.77) or the sham treatment (0.0116 +/- 0.0648 Hz, p=0.293). The change caused in SDNN by sham (0.0116 +/- 0.0648 Hz) compared to the change caused by the time control (0.157 +/- 0.0756 Hz) also did not differ significantly; p=0.069 (Figure 7).

Frequency Domain

When comparing the effect of each intervention to each other in the frequency domain, LF had no significant differences, but OMT was significantly different in the HF.

Low Frequency (LF): The change to LF caused by OMT (-0.0000141 +/- 0.0000894 Hz) compared to the change caused by sham (0.0000456 +/- 0.000147 Hz) was not significant; p=0.729. The change caused by OMT compared to the change caused by the time control (0.000232 +/- 0.000178 Hz) was not found to be significant; p=0.374. The change caused by sham compared to the change caused by the time control was not found to be significant either; p=0.651 (Figure 8a).

High Frequency (HF): OMT significantly differed from sham and the time control, while the sham and the time control did not significantly differ from one another in the HF range. The change caused by OMT (0.000167 +/- 0.0000869 Hz) compared to the change caused by sham (0.000115 +/- 0.000126 Hz) was significantly greater; p=0.038. The change caused by OMT compared to the change caused by time control (0.0000565 +/- 0.000109 Hz) was also significantly greater; p=0.047. The change caused by sham compared to the change caused by the time control was not significantly different; p=0.891 (Figure 8b).

Low Frequency/High Frequency: The change caused by OMT (-0.791 +/- 0.659) compared to the change caused by time control (0.664 +/- 0.418) was significantly different; p=0.003. The change caused by OMT compared to Sham (0.290 +/- 0.214) was not significantly different; p=0.113. Neither was the change caused by sham different from the change caused by the time control; p=0.444.

CHAPTER 4

DISCUSSION

SUMMARY OF FINDINGS

This study collected demographic and heart rate variability (HRV) data from nineteen subjects for three different experimental protocols: Osteopathic Manipulative Treatment (OMT), Sham, and a Time Control. The baseline HRV for all subjects before undergoing every protocol was found to be the same. The sham protocol did not produce a significant change in HRV for any parameter measured: the standard deviation of normal-to-normal (SDNN) intervals, low frequency (LF) HRV, high frequency (HF) HRV, or the ratio LF/HF. The time control protocol did not produce a significant change in SDNN, LF HRV, HF HRV or LF/HF. OMT produced a statistically significant change in SDNN, p=0.005; and trended toward producing a significant change in HF HRV, p=0.071; while it had no significant effect on LF or LF/HF; p= 0.876 and p=0.293, respectively.

When comparing the change in one protocol to the change in another, the OMT intervention was statistically different from sham and the time control in HF HRV, p=0.038 and p=0.047, respectively. Thus, these data support the hypothesis that cervical manipulation can evoke an increase in vagal control of heart rate independent of a placebo or sham effect, but it does not appear to affect sympathetic control based on the HRV measures obtained. The difference between the change caused by OMT and that caused by the time control protocol in the LF/HF parameter was also significant; p=0.018.

DEMOGRAPHICS

This was a homogeneous group of young, healthy, adult subjects, with a standard deviation in age of 2.5 years and standard deviation in BMI of 3.75 kg/m2. The cohort was 94.7% Caucasian.

EFFECTS ON HRV

Significance of Baseline Data

The baseline HRV data supports the finding of homogeneity in the study population. The crossover design of this study controlled for individual differences between subjects by having them participate in all protocols. The baseline data also supports the ambulation and twenty-minute quiet rest aspects of each protocol, to allow each subject to reach an autonomic baseline prior to data collection independent of the order in which the subject underwent each intervention.

Changes Due To Sham and Time Control

The sham protocol was designed to control for the possible effect of a human simply coming within skin-to-skin contact in the area of the OMT protocol. The autonomic nervous system (ANS) reacts to moments of emotional stress, as well as physical contact, and therefore this protocol was included to determine whether or not the stress of having a stranger touch the subject's neck would influence their HRV. The time control protocol was included to observe the effect of the continued quiet, supine rest beyond the twenty-minute preparatory time allowed for in the protocol design. This controlled for any naturally occurring changes in HRV associated with lying quietly for this time period.

Finding that the sham protocol produced no significant difference in SDNN, LF HRV, HF HRV, or LF/HF provides evidence that human touch, under the research conditions of the sham protocol, does not affect HRV. This finding could then be extrapolated to imply that the kind of human touch found in the sham protocol does not affect autonomic control of heart rate. This provides a basis to conclude that the OMT manipulation in the same region had an effect independent of simple contact of this region of the neck and lower skull.

The time control protocol did not produce a significant change in SDNN, LF HRV, HF HRV or LF/HF. This indicates that the additional fifteen minutes the subject spent on the table did not significantly influence these measurements of HRV. There was, however, a significant difference between the changes in LF/HF caused by the time control when compared to OMT. This ratio is a mathematical manipulation theorized to better isolate the sympathetic contribution to HRV. HF variation has been well-established to be due to the influence of the parasympathetic nervous system (PNS) only. LF variation has been shown to be effected by both the PNS and the SNS. The calculation of a LF/HF ratio thereby normalizes the LF for HF power and presumably reveals a measure of SNS control. However, this interpretation remains controversial and imprecise. This is due, in part, to the fact that changes in HF power do not necessarily produce directly proportional changes in LF power. Thus, the PNS contribution to each frequency is also incongruent. Since the exact relevance and meaning of this measurement has not been well established, the interpretation of this particular finding is unclear. The question of why this finding was not consistent throughout all three treatment arms remains unknown. One possible explanation can be found when examining the baseline data for LF in the time control group. The baseline data set for LF approached a significant difference, $p = 0.076$, with the time control group starting at a lower value. Its increase over time could be a sign of normalization toward the baseline data for the other two interventions. In addition to this increase, the decrease seen in the LF of OMT accentuated the overall decrease between the changes in LF/HF caused by OMT and time control. A possible explanation of the decrease in LF for the OMT protocol will be addressed in the next section.

Change Due To OMT

This study was conducted to investigate the effects of OMT on the PNS. As discussed above, the theoretical approach to the use of OMT involves treating somatic dysfunction found in areas known to affect the SNS, PNS, and the lymphatic vasculature. The soft tissue techniques used on each subject are used to prepare tissues for further osteopathic manipulative medicine techniques and mobilize the soft tissues in general. The sub-occipital decompression technique focuses its intention on the musculature found directly inferior to the occiput. This area is believed to be critical to treat for a large portion of the PNS because this is where the vagus nerve exits the cranium. The technique works to release tension held by all the muscles directly contacting the occiput posteriorly. The forces applied in this technique are also theorized to free the motion of the occiput on all its articulations – including its articulation with the temporal bone. This articulation is the location where the vagus nerve exits the cranium and therefore the reasoning behind the theorized effect on PNS control of heart rate.

The OMT intervention evoked a significant increase in the SDNN; $p=0.005$, and an increase in the HF HRV that trended toward significance; $p=0.071$. The significant change in SDNN in the OMT arm of the study, and not in the sham or time control, supports the part of my hypothesis that OMT will increase HRV, and particularly the PNS component of HRV. The more specific measure of the PNS, HF HRV, did not show a statistically significant change enough to support my hypothesis. However, the p-value of 0.071 does indicate a possible trend might be present. I believe this finding to be a significant indication for further research because the small sample size may be limiting my ability to detect this possible difference. This result is further supported by the finding that the *change in HF* associated with OMT was significantly greater when compared to sham or time control.

The decrease seen in LF after OMT, and the following decrease in LF/HF, could be viewed as a reciprocal effect. The OMT protocol was designed to increase the PNS control of HRV. Many ANS reflex arcs are know to cause a decrease in one side as the other side increases. Therefore, the decrease in LF after OMT, may be thought to represent the reciprocal action of the ANS.

LIMITATIONS

The obvious limitation to this pilot study, as mentioned above, was the sample size of n = 19. The statistical power estimates based on the data ranged from 0.60-0.84 and thus the study, as performed, was somewhat underpowered. This limitation is compounded by the fact that this study was focused on measures of potentially small change, that is the expected effect may be small in many subjects. In quiet resting healthy subjects the ANS is shifted to a predominance of high PNS activity and control. Therefore, it is likely that interventions designed to increase PNS further may not be very effective under these conditions. Likewise, since SNS activity is very low under these conditions, the effect to decrease SNS activity may also be very limited in magnitude. With respect to the amount of change, the homogeneous healthy, young adult population might also be a source of limitation. Sub-occipital decompression is used on somatic dysfunction; however, the procedure can be performed in the absence of dysfunction. This study population my not have had significant somatic dysfunction to begin with, and therefore, the change detected may have been smaller than that found in subjects with more significant dysfunction.

These healthy subjects may be presumed to have healthy autonomic nervous systems; and therefore a large change in HRV less likely.

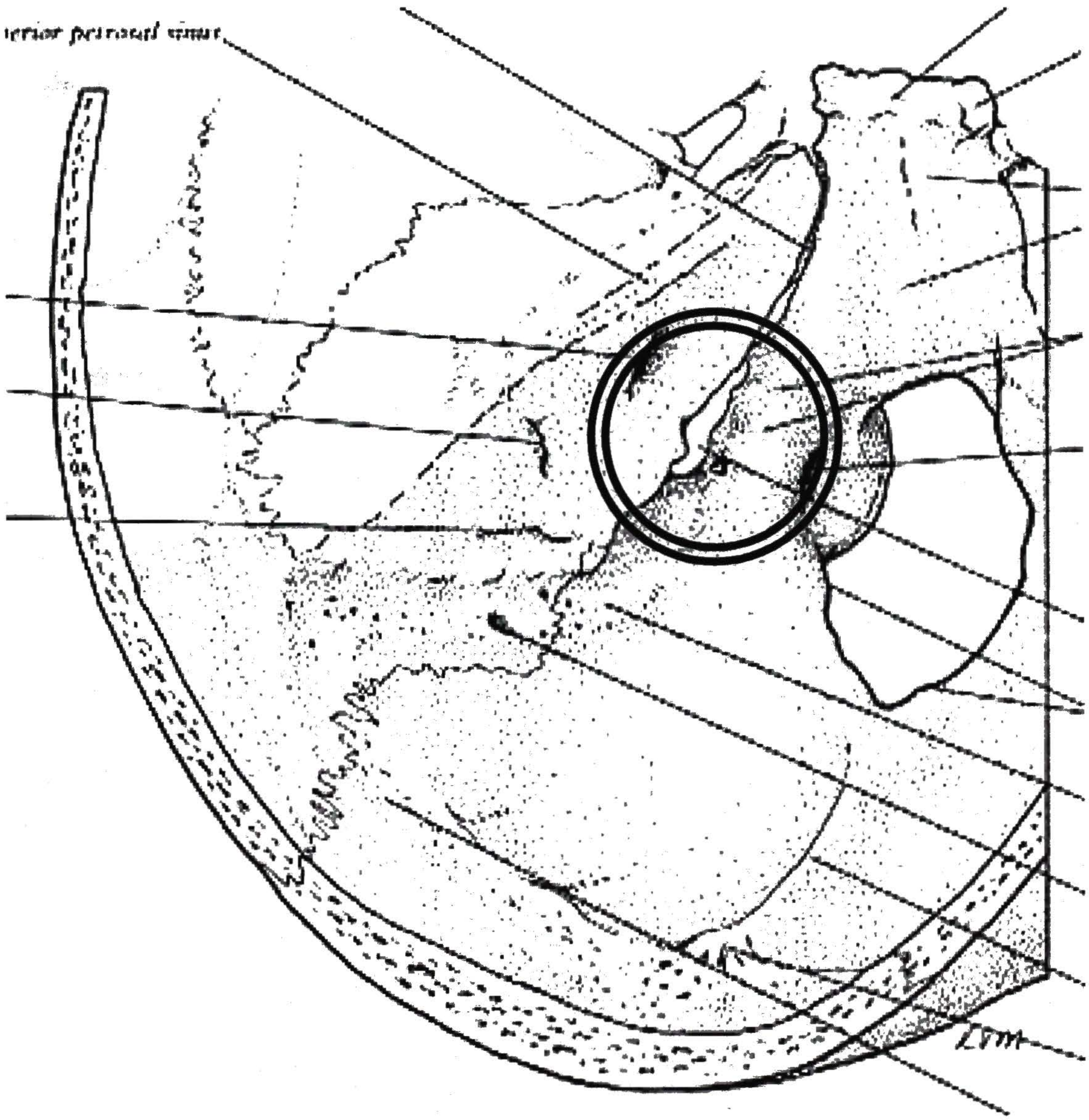
CONCLUSIONS AND FUTURE DIRECTION

From this study I am able to say that the human contact performed in the sham protocol does not affect HRV. The results concerning the effects of OMT on HRV are not as definitive, but demonstrative of a trend worth exploring in further studies. Nevertheless, the data support an effect of this form of cervical OMT on PNS control of heart rate in young healthy subjects despite the limitations noted above. The immediate goal for the future is to complete studies on an additional group of subjects in order to resolve the suboptimal statistical power. No adverse reaction occurred during this study, on healthy subjects, and could therefore be used to argue for moving the study of OMT on the ANS onto a population of a specific disease process, such as depression or cardio vascular disease. These disease states, shown to have a decreased HRV, might also demonstrate a larger change in HRV, thus providing data with more power concerning OMT and the ANS.

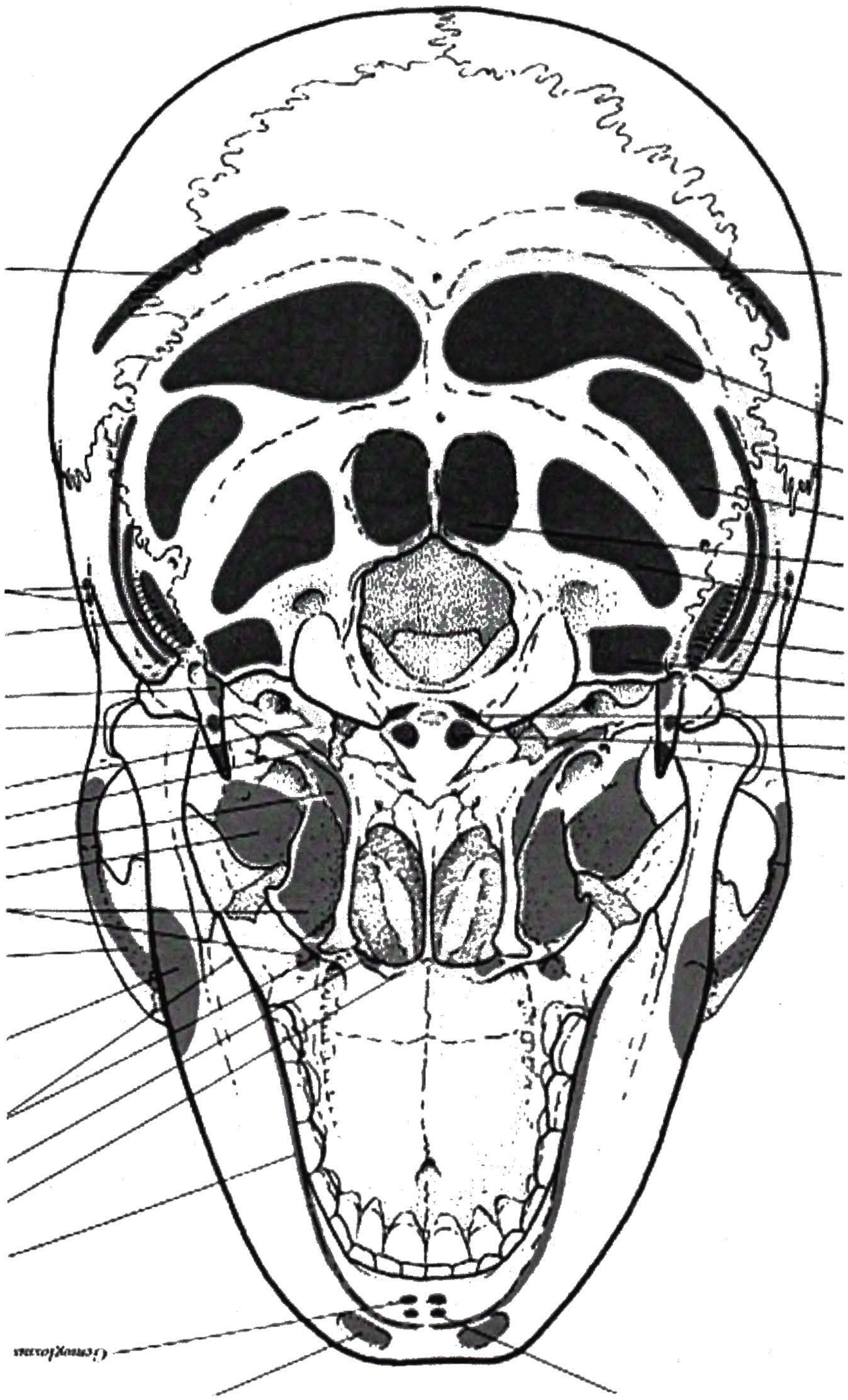
A possible change to the study design would be to control respiration of the subjects. This has been shown to increase the HF signal in previous studios (Eckberg, 2000); and, by having the subject breath to a metronome, they would have something mentally engaging them and reducing the likelihood of sleep during the time control.

APPENDIX

Anatomy Plate 1: Jugular Foramen (Double Circle) (*Gray's Anatomy* 1989)



Anatomy Plate 2: Muscular Attachment to Occiput (*Grey's Anatomy* 1989)



Anatomy Plate 3: Posterior Cervical Anatomy (Netter)

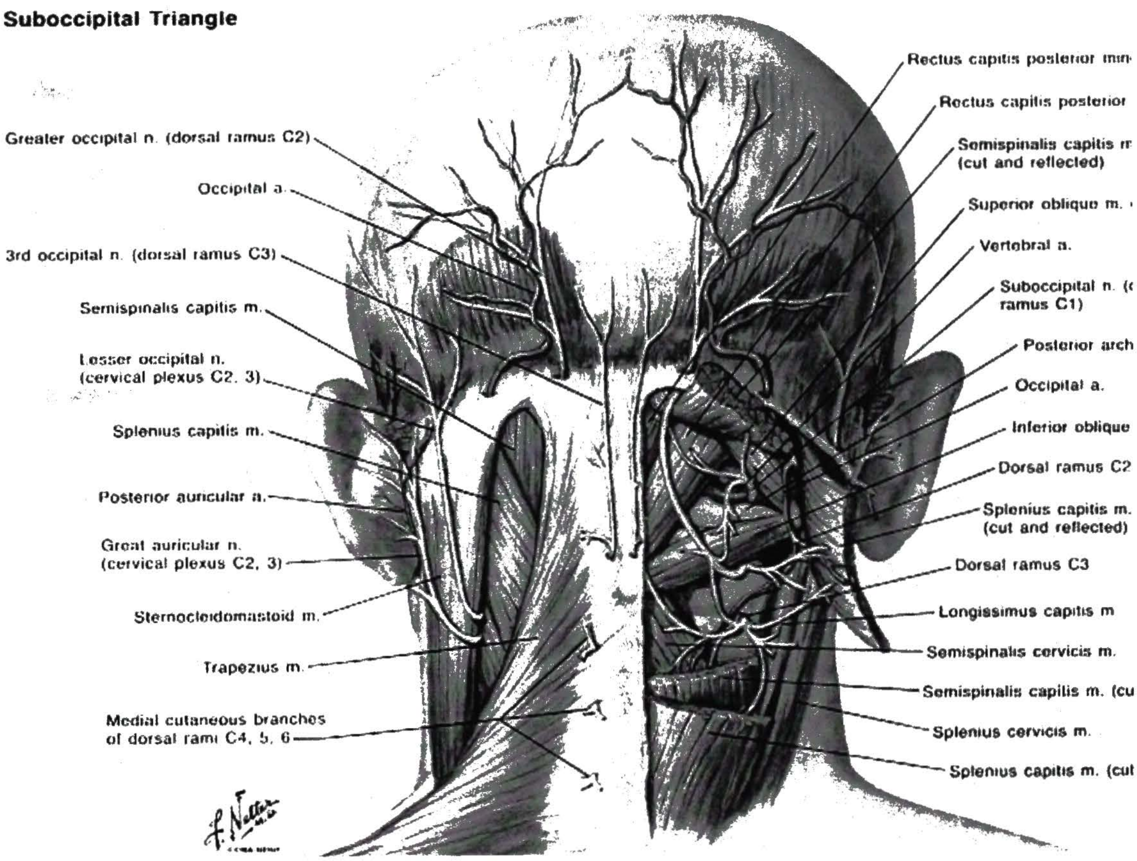


TABLE 1: Demographics

	Gender	Age	BMI	Ethnicity
	Female	25	19.67	Caucasian
	Female	25	20.18	Asian
	Female	25	20.60	Caucasian
	Male	24	29.53	Caucasian
	Female	31	25.66	Caucasian
	Female	23	19.74	Caucasian
	Male	26	27.71	Caucasian
	Female	22	24.03	Caucasian
List of Subjects	Female	23	20.70	Caucasian
	Female	22	21.63	Caucasian
	Female	24	20.60	Caucasian
	Female	30	18.56	Caucasian
	Male	24	29.82	Caucasian
	Male	29	25.85	Caucasian
	Female	24	19.24	Caucasian
	Male	26	20.49	Caucasian
	Female	27	22.94	Caucasian
	Female	26	25.40	Caucasian
	Male	26	28.70	Caucasian
Descriptive Statistics of Group				
Mean		25.37	23.21	
Median		25	21.63	
Standard Deviation		2.5	3.75	
Range		9	11.26	

Figure 1

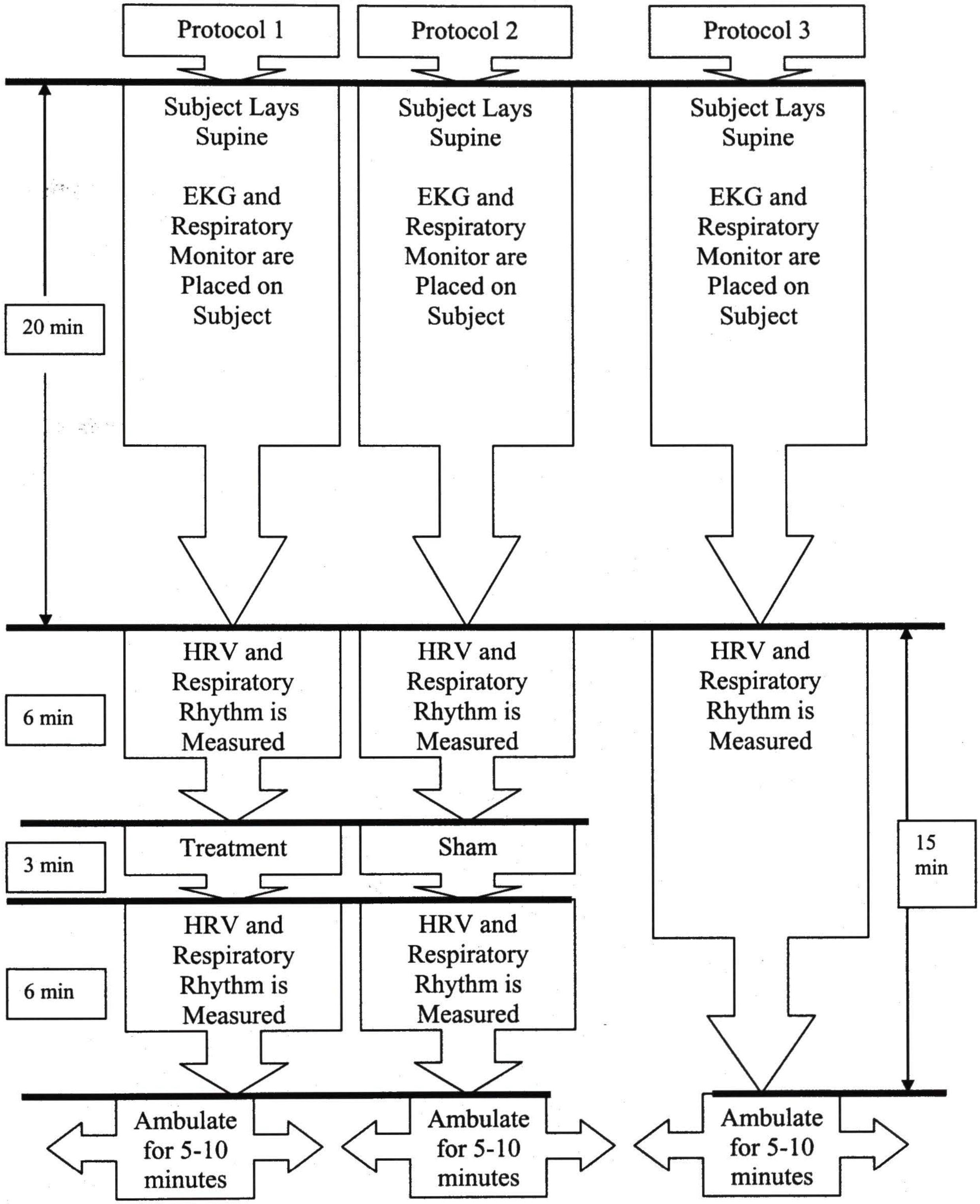

Protocol 1
Protocol 2
Protocol 3
20 min
Subject Lays Supine
EKG and Respiratory Monitor are Placed on Subject
Subject Lays Supine
EKG and Respiratory Monitor are Placed on Subject
Subject Lays Supine
EKG and Respiratory Monitor are Placed on Subject
6 min
HRV and Respiratory Rhythm is Measured
HRV and Respiratory Rhythm is Measured
HRV and Respiratory Rhythm is Measured
15 min
3 min
Treatment
Sham
6 min
HRV and Respiratory Rhythm is Measured
HRV and Respiratory Rhythm is Measured
Ambulate for 5-10 minutes
Ambulate for 5-10 minutes
Ambulate for 5-10 minutes

Figure 2: Comparison of Baseline Data

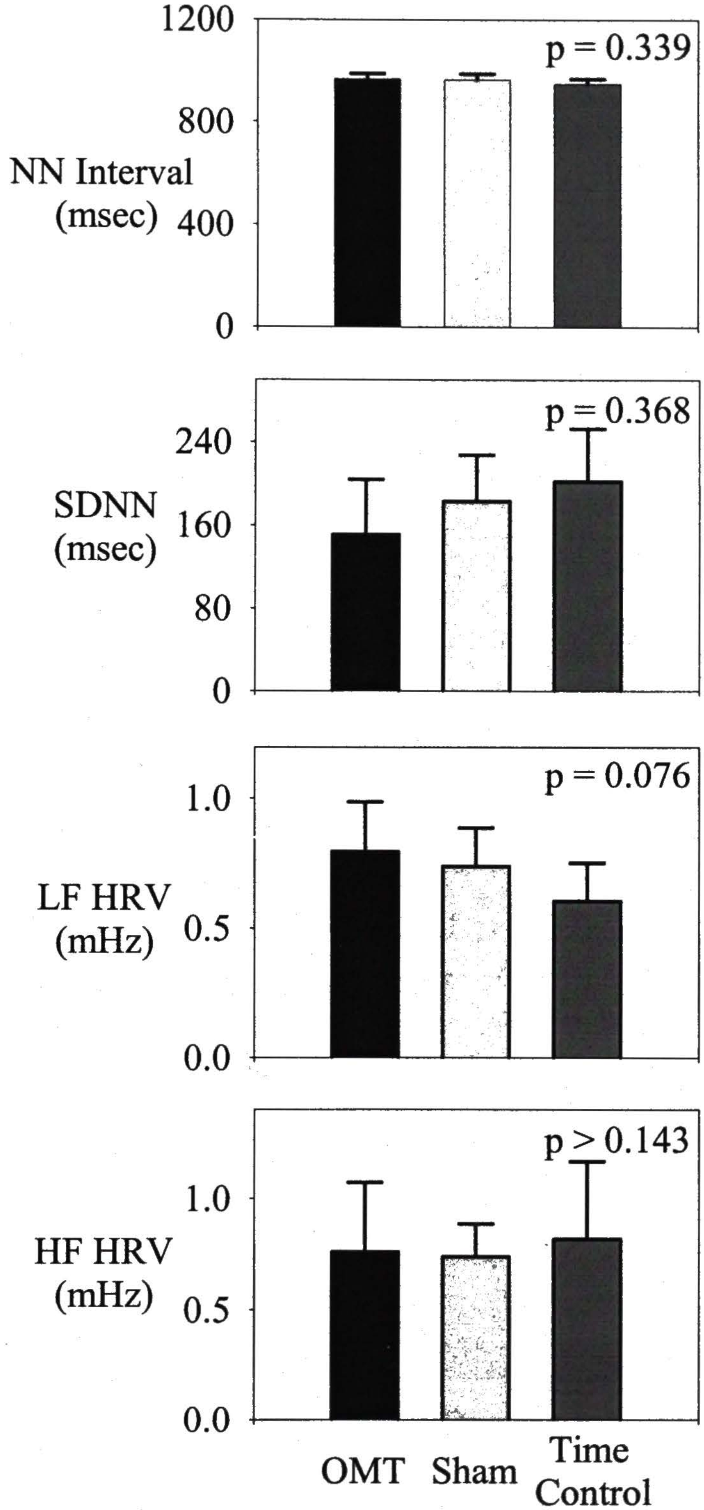


Figure 3: Pre/Post Interevention Time Domain: SDNN (sec)

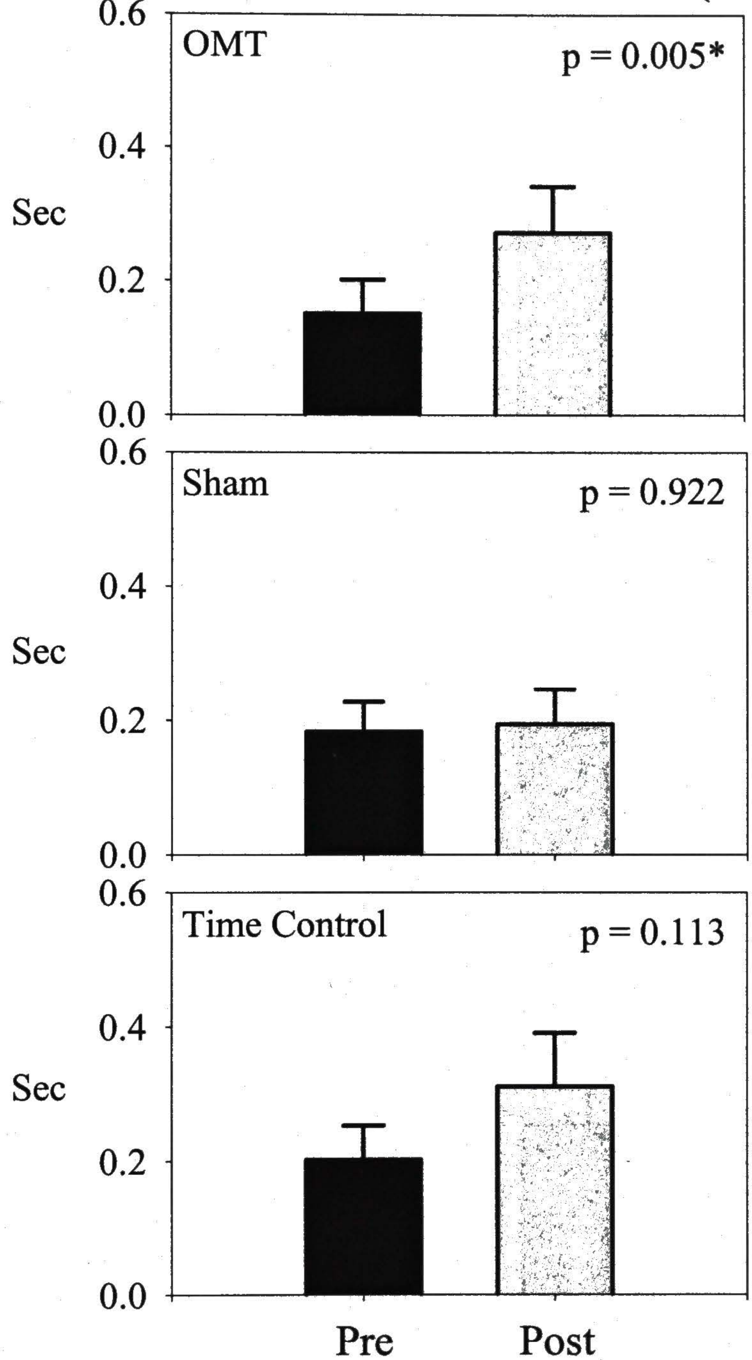


Figure 4: Pre/Post Intervention Frequency Domain: LF (mHz)

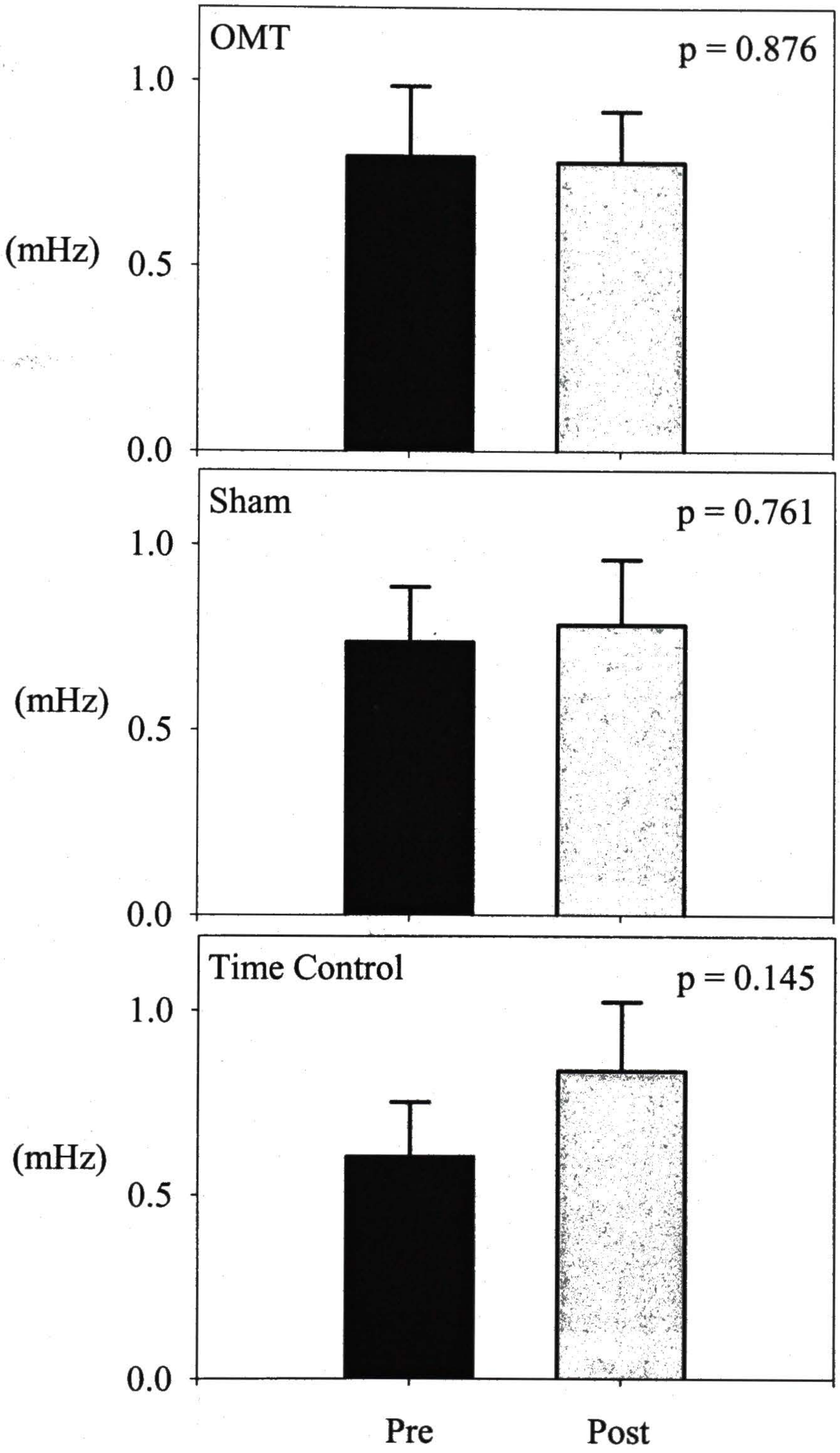


Figure 5: Pre/Post Intervention Frequency Domain: HF (mHz)

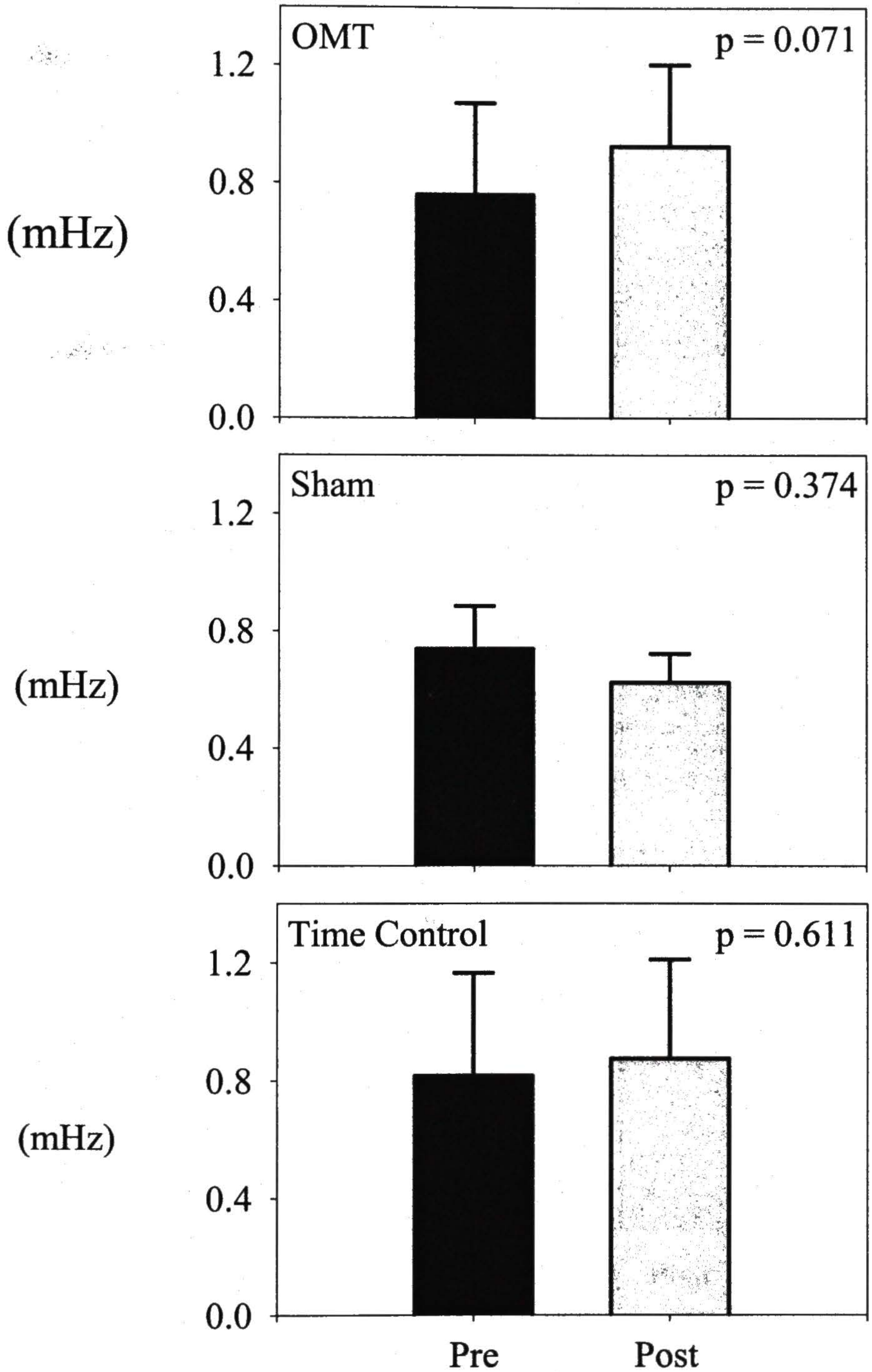


Figure 6: Pre/Post Intervention Frequency Domain: LF/HF

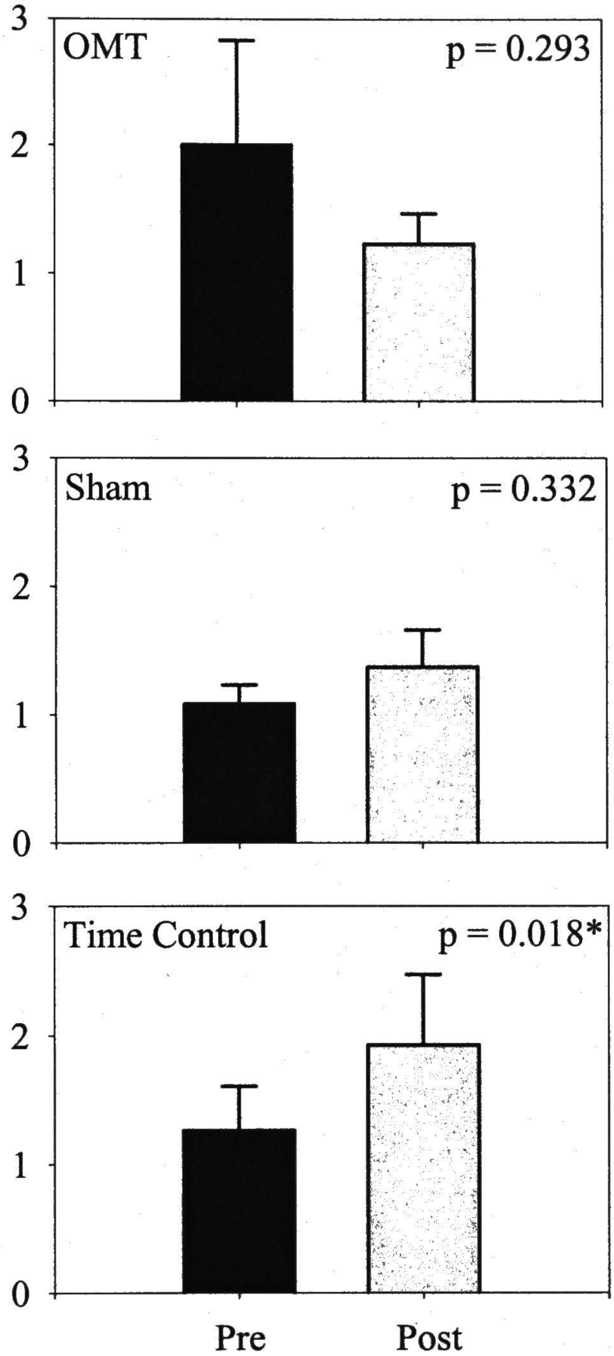


Figure 7: Effect Change Due To Intervention: Time Domain: SNDD (msec)

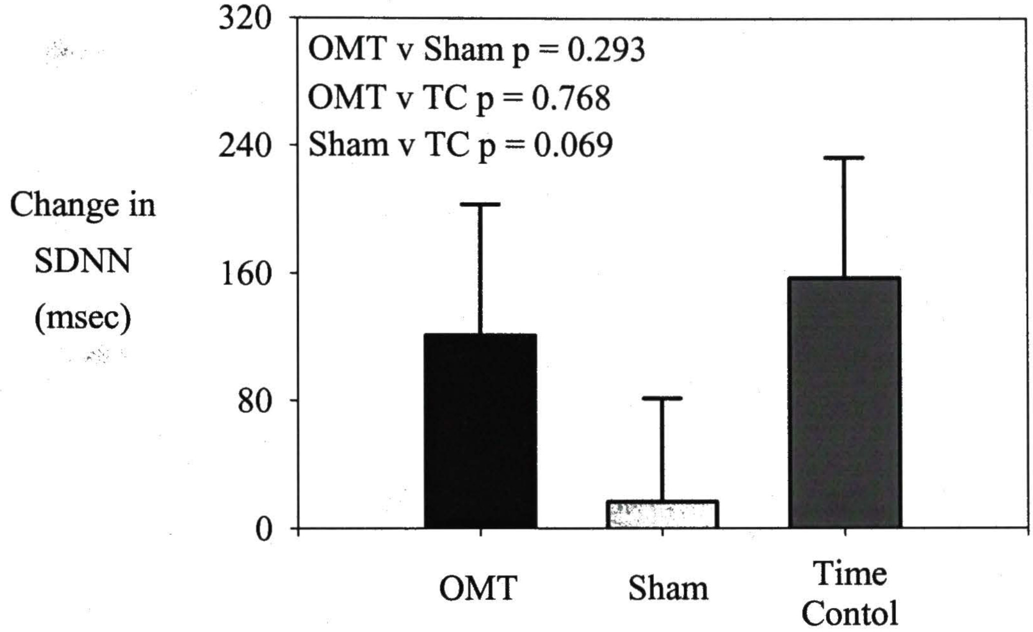
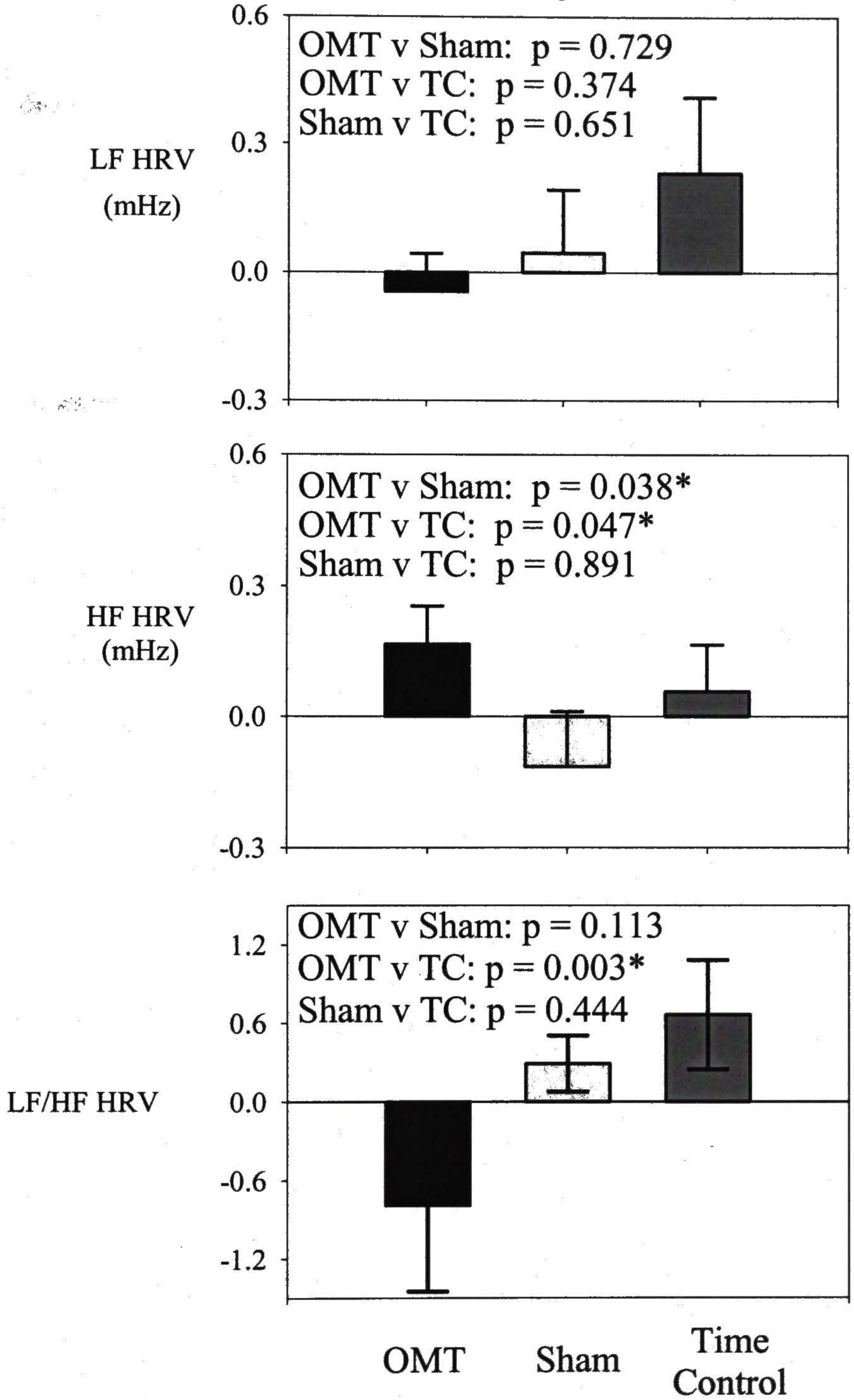


Figure 8: Effect Change Due To Intervention: Frequency Domain



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