

**DISCRIMINATION OF CARDIAC HEALTH AND DISEASE
BY ASSESSMENT OF HEART RATE VARIABILITY:
WAVELET VS. FAST FOURIER TRANSFORMATION**

A Thesis

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**by
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DEDICATION

I would like to dedicate my thesis to my wonderful parents, Matthew and Joyce DeRouen. They have always been there to love, support, and guide me. God has blessed me with two loving parents who worked hard to provide me with everything necessary for me to become the individual I am today. I am so very thankful for that blessing and for the example you both were to me over the years. I would not have made it this far without your motivation and dedication to my success. Thank you, mom and dad, I love you both.

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ABSTRACT

The autonomic nervous system (ANS) modulation of the heart is of clinical importance because of its relevance to risk of life threatening arrhythmic events. Decomposition of heart rate variability (HRV) has been used to quantify ANS control of the heart. The traditional method for frequency analysis has involved the use of fast Fourier transformation (FFT). However, heart rate data typically violate assumptions of the FFT. Therefore, the assessment of HRV may benefit from other, potentially more suitable, mathematical approaches. For example, the discrete wavelet transformation (DWT) appears to have promise with respect to its ability to discriminate between healthy and diseased populations. Therefore, the purpose of this thesis was to examine the extent to which the FFT can discriminate between a control group and heart failure patients (CHF) in comparison to DWT. Seven CHF (mean +/- standard deviation, age: 51.9 +/- 17.6 yrs) and eight age-matched controls (49.5 +/- 17.9 yrs) were evaluated. HRV was evaluated during 5 minutes of supine spontaneous breathing (SB) and supine paced breathing (PB) (0.2Hz). The ECG data were sampled at 200 Hz, converted to heart rate tachograms, and subjected to frequency analysis via FFT and DWT. The FFT approach did not reveal group differences in HRV, while the DWT revealed group differences in LF/HF during SB ($p < 0.05$) and PB ($p = 0.053$). With respect to breathing condition, only the FFT revealed that PB resulted in a decrease in low- to high-frequency ratios ($p < 0.05$), and an increase in standard deviation of normal R-R intervals. These results support further consideration of both methods of analysis, as they each appear to provide unique information about HRV.

CHAPTER 1—INTRODUCTION

The last two decades have witnessed the recognition of a significant relationship between autonomic nervous system function and cardiovascular mortality, including sudden cardiac death. Experimental evidence for an association between propensity for lethal arrhythmias and signs of either increased sympathetic or reduced vagal activity has spurred efforts for the development of quantitative markers of autonomic activity (Task Force, 1996).

Heart rate variability (HRV) represents one of the most promising such markers. Autonomic markers such as HRV are receiving increasing attention for the identification of patients at high risk. There is an increasing need for the development of sensitive tools for risk factor stratification because of the danger of cardiac arrhythmias and sudden cardiac death. It is important to identify in what populations these risks are most prominent or pose a great amount of caution. The most crucial application of HRV measurement is in its prognostic indication for sudden cardiac death. Typically, low HRV has been associated with a higher risk for sudden cardiac death (Futterman & Lemberg, 1994). Therefore, developing the most appropriate tools for analysis of HRV is important for risk stratification. Determining risk of cardiac events is an asset in treatment and management of disease.

1.1 Heart Rate Variability Defined

HRV is a non-invasive measure of autonomic nervous system balance. This method has been advanced as one capable of estimating relative parasympathetic and sympathetic neural contributions to the modulation of the heart (Notarius et al., 1999). HRV is measured in the time domain by familiar approaches to quantifying variability,

such as in the case of standard deviation of R-R intervals or less frequently, of instantaneous heart rate and R-R intervals. The R-R interval is the time duration between consecutive R waves of an ECG. HRV has been quantified in the frequency domain by way of fast Fourier transformation (FFT) of successive R-R intervals. Meaningful analysis of HRV is dependent on the integrity of the basic cardiac signal input. This cardiac input is usually in the form of the electrocardiogram, which has been widely accepted as a statistical measure of HRV. Action potential propagation through the heart generates electrical currents that can be detected at the surface of the body. The record of these electrical events is called the electrocardiogram, abbreviated either ECG or EKG. Collectively, the ECG is a composite recording of action potentials produced by all the heart muscle fibers during each heartbeat (Tortora & Grabowski, 2000).

Depression of HRV has been observed in many clinical settings including congestive heart failure, autonomic neuropathy, myocardial infarction, heart transplantation, and other cardiac and noncardiac diseases. However, clinical implication of HRV analysis has been clearly recognized in only two of these clinical conditions: (1) as a predictor of risk of arrhythmic events or sudden cardiac death after acute MI and (2) as a clinical marker of evolving diabetic neuropathy (Stys & Stys, 1998). In population studies, decreased HRV has had predictive value for mortality among healthy adults. It is a well-established risk factor for arrhythmic events and mortality among post-MI patients but has only moderate sensitivity and specificity (Stein & Kleiger, 1999). The role of HRV assessment has also been recognized and is still being applied in the evaluation and management of heart failure.

Although autonomic dysfunction can pose a threat to physiological health, there are methods of intervention that have proven successful in decreasing negative effects of autonomic imbalance. Common medications prescribed for these conditions include calcium-channel blockers, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, diuretics, and digitalis drugs. Medications for treatment of hypertension, heart failure, diabetes and other conditions related to autonomic dysfunction help to control symptoms and prevent exacerbation of these symptoms. Other types of medical intervention include reconstructive surgery, heart transplants, and placement of pacemakers.

Of particular relevance to the Kinesiologist is the use of physical activity as a treatment strategy for the purpose of improving health outcomes and reducing cardiovascular risk. Formal exercise and physical activity patterns have been associated with improved HRV profiles in a variety of populations. More specifically, exercise appears to increase vagal activity and attenuate sympathetic modulation of the heart (Curtis & O'Keefe, 2002).

While all these treatments have been proven effective in many cases, it is crucial that efforts are continued in order to evaluate treatment strategies. Measurement of HRV can play an important role as a tool in prediction of disease and for risk stratification. However, in the terms of treatment, it can also be used to determine the effectiveness of the various strategies used to treat dysautonomia.

1.2 Justification for Research

Previous literature demonstrates that HRV assessment can be an effective clinical tool. It can prove effective in assessing ANS function, as well as assessing effectiveness

of the various approaches to treatment. However, there are pitfalls and complexities involved in the measurement, analysis, and interpretation of HRV. The more common tools used for HRV measurement tend to discriminate on merely a population basis. It is our concern that analysis tools may be more beneficial if they separate on an individual basis. Another concern is the ability of this technique to distinguish between healthy individuals and those with autonomic dysfunction. The need to distinguish between these populations would provide the means for enhanced as well as more specific treatment strategies. The method in which HRV is analyzed may determine whether HRV can be an effective discriminatory tool for separation between healthy and diseased populations.

1.3 Purpose of the Study

Therefore, the purpose of this study was to examine the potential of two different types of HRV analyses in order to determine which is a more powerful tool for discriminating between cardiac diseased and healthy populations. The only study to specifically address this issue was performed using multiresolutional wavelet transform technique. Ashkenazy et al. (1998) demonstrated that it is possible to distinguish with complete certainty between healthy individuals and those with various cardiac nervous system dysfunctions. It is apparent, by the lack of literature, that more data are needed to confirm the important findings of Ashkenazy et al. Thus, it was our intention to discover the ability of our laboratory to observe the same phenomenon.

1.4 Hypothesis

Based on the findings of Ashkenazy et al. (1998), we hypothesized that the use of the wavelet transform in comparison to the FFT to analyze HRV data would be a more powerful tool for discrimination between the cardiac diseased and the apparently healthy

individuals in this study. Furthermore, there are some shortcomings of the Ashkenazy model that we attempted to address by expanding the approach to include an index of sympathovagal balance.

1.5 Limitations of the Study

Overall, the limitations of this particular study evolved around some aspect of the subject population tested. Although there were no significant characteristic differences between groups, the mean weight was higher in the CHF group. Also, the control group may not have been extremely well matched to the CHF group. The individuals were matched according to age. They were not matched based on gender, ethnicity, or geographical location. All of which have been shown to be influential factors. Therefore, it is possible that the fact that the majority of the participants (N=15) were females (n=10) produced some bias. Finally, the medications that the CHF individuals were taking may have impacted the results.

CHAPTER 2—REVIEW OF LITERATURE

2.1 The Autonomic Nervous System

The autonomic nervous system (ANS) is the part of the nervous system that functions to sustain life by controlling the heart, lungs, digestive system, blood pressure, immune system, along with other human functions. It is considered the motor division of the peripheral nervous system. The ANS has two major divisions (Figure 2.1): the parasympathetic and sympathetic nervous system. These two systems originate from and are activated by different sections of the spinal cord, brain stem, and hypothalamus. Also, portions of the cerebral cortex and limbic cortex can transmit impulses to the lower centers and influence autonomic control. The ANS also often operates by means of visceral reflexes. Visceral reflexes are the sensory signals entering the autonomic ganglia, cord, brain stem, or hypothalamus that can elicit appropriate reflex responses directly back to visceral organs to control their activities (Guyton & Hall, 1996).

The effects of the sympathetic and parasympathetic systems are often antagonistic, but both systems always function together (Wilmore & Costill, 1999). Most body organs are innervated by both divisions of the ANS. The balance between the sympathetic and parasympathetic activity or “tone” is regulated by the hypothalamus. Typically, the hypothalamus turns up sympathetic tone at the same time it turns down parasympathetic tone, and vice versa. The two divisions can affect body organs differently because their neurons release different neurotransmitters. Also, effector organs possess different adrenergic (sympathetic) and cholinergic (parasympathetic) receptors, which determines how the ANS affects them.

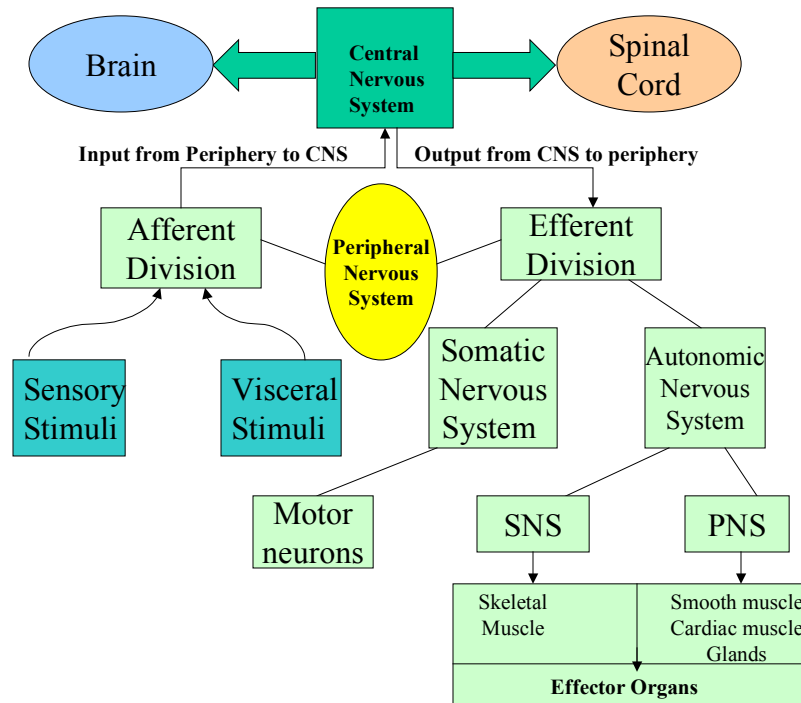


Figure 2.1 The Autonomic Nervous System

The sympathetic nervous system (SNS) releases the neurotransmitter responsible for initiating the “fight-or-flight” response. During physical or emotional stress, the sympathetic division of the ANS dominates the parasympathetic division. It prepares the body for strenuous physical activity in the face of emergency or stressful situations. This physiological response occurs with an increasing heart rate, more forceful heart contractions, and an increase in blood pressure. All of these responses occur in an effort to provide increased flow of oxygenated, nutrient-rich blood to skeletal muscles in anticipation of strenuous physical activity. Also, the pupils dilate and the eyes adjust for far vision, which enables one to make a quick visual assessment of the entire threatening scene. Sweating is promoted, and unessential activities like digestive and urinary activities are inhibited by the SNS. Some structures, such as sweat glands, the kidneys, most blood vessels, and adrenal medulla, receive sympathetic innervation only. Along

with physical exertion, a variety of emotions—such as, embarrassment, fear, or rage—stimulate the SNS.

In contrast to the “fight-or-flight” activities of the sympathetic division, the parasympathetic nervous system (PNS) enhances the “rest-and-digest” activities (Tortora & Grabowski, 2000). The PNS is dominantly operated by the vagus, or tenth cranial nerve. Vagal nerve control supports body functions that conserve and restore energy during rest and recovery periods. In quiet intervals absent of stressful stimuli, parasympathetic impulses to the digestive glands and smooth muscle of the gastrointestinal tract predominate over sympathetic impulses. This predomination allows energy-supplying food to be digested and absorbed. While the parasympathetic is dominating the “at rest” body functions, it also reduces those functions that support physical activity.

2.2 Autonomic Control of the Heart

The chronotropic (rate) and inotropic (contractility) behavior of the heart come under the influence of the autonomic nervous system. Sympathetic mediated and parasympathetic mediated activities, however, are mitigated through very different mechanisms. The membrane processes of the cardiac sinoatrial (SA) node controls the normal rhythm of the heart. The membrane processes are modulated by innervation from both the sympathetic and parasympathetic divisions of the ANS. The nerve processes of the PNS are composed of two neurons, each of which releases acetylcholine (ACH). When ACH is released by postganglionic parasympathetic terminals at the sinoatrial node, it slows the rate of SA node discharge and depolarization (Bernston et al., 1997).

This decreased speed of SA node happens when the ACH binds to the muscarinic cholinergic receptors to activate potassium channels.

Sympathetic nerve processes are also composed of two neurons. The first releases ACH (like the PNS), but the second usually releases norepinephrine (noradrenaline). The release of norepinephrine from the sympathetic terminals of the SA node speeds the SA node rhythm. The speed is increased as a result of the β_1 receptor-mediated second messenger intracellular signals. Chemical mediators released from the autonomic nerve endings bind to receptors in the cell membranes of target tissues. The mediators frequently change postsynaptic target tissue membrane permeability to ions. ACH slows the heart by decreasing the resting membrane potential. Norepinephrine, which is predominantly released by SNS neurons speeds the heart via stimulation of cation influx. However, the initial transmitter substances can only cause temporary changes in neurons. The ion channels are not suitable for causing prolonged postsynaptic neuronal changes because these channels close within milliseconds after the transmitter substance (norepinephrine or ACH) is no longer present (Guyton & Hall, 1996).

Many functions of the ANS require prolonged changes in neurons after the initial transmitter substance is gone. In many instances, this prolonged action is achieved by activating a “second messenger” chemical system inside the postsynaptic neuronal cell itself. Then the second messenger causes the prolonged effect (Guyton & Hall, 1996). One type of second messenger system is one that uses a group of proteins called G-proteins (Figure 2.2). The G-protein is attached to the portion of the receptor protein that protrudes to the interior of the cell. The G-protein consists of three components: the alpha (α) which is the activator portion of the G-protein, and beta (β) and gamma (γ),

components that attach the protein to the inside of the cell adjacent to the receptor protein.

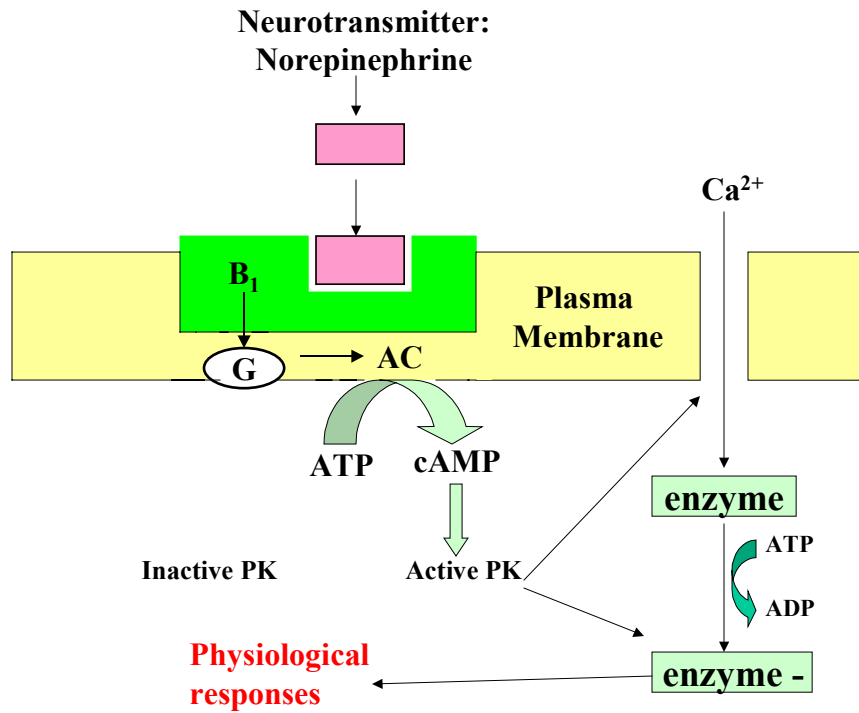


Figure 2.2-Second Messenger System with G-protein

Along with the neurotransmitter actions, the chronotropic state of the heart can be modulated by a variety of factors. However, direct autonomic innervation of the SA node is the main influence to which the chronotropic activity of the heart is attributed. The sympathetic system can indirectly regulate heart rate through the release of adrenomedullary catecholamines. Other humoral factors that may influence HRV include variations in the renin-angiotensin system (Akselrod et al., 1981).

2.3 Measurement of the Autonomic Nervous System

There are various methods employed in measuring ANS activity. Some approaches involve blood pressure and heart rate measurements. Measurement of blood pressure and heart rate responses to stressful stimuli in a laboratory environment is a

widely used method for investigating autonomic control (Grassi et al., 1996). However, there are limitations involved with using stressful stimuli because of the difficulty in standardizing them. Also, laboratory stressor maneuvers require continuous monitoring and are not always powerful enough to initiate measurable changes.

Measuring cardiac norepinephrine spillover has been used as an index of sympathetic nerve firing rate. Although cardiac sympathetic activity may be clinically important, some methods of measurement, such as assessing cardiac norepinephrine overflow, are invasive and unsuitable for widespread application or repeated measurement (Kingwell et al., 1994). Kingwell et al. show that in pure autonomic failure and soon after transplantation, cardiac norepinephrine spillover was negligible, and HRV was low. This proposes another disadvantage of this method of measurement. However, the evidence that plasma norepinephrine concentration is significantly and independently correlated with mortality in patients with congestive heart failure raises the possibility that this simple measurement might provide a useful guide to clinical decision-making in individual patients. Such predictive tests would be helpful in personal planning as well as in selecting therapeutic strategies, including new drugs and heart replacement procedures (Rector, Olivari, Levine, Francis, & Cohn, 1987).

While measurement of catecholamines may prove beneficial in providing information in some clinical settings, there are other concerns with the use of this technique. Recently, Forslund et al. (2002) assessed the prognostic impact of autonomic activity reflected by catecholamines and HRV in patients with stable angina pectoris. Forslund et al. found low HRV to be a predictor of cardiovascular death and that the analyses of catecholamines carried no prognostic information. Furthermore, an increase

in catecholamine levels does not automatically indicate autonomic dysfunction. Other factors, such as reuptake or clearance of catecholamines could also be the cause of the excess in these levels.

Measurement of heart rate and evaluation of its rhythmicity have been used for a long time as a simple clinical indicator (Ashkenazy et al., 1998). Variation and fluctuation of the heart rate in relation to mean heart rate have been shown to be a function of cardiorespiratory physiology (Dreifus et al., 1993). It has been known for several decades that enhanced vagal tone has a salutary effect on the electrophysiologic properties of the ventricle to prevent the emergence of life-threatening ventricular arrhythmias in certain situations. Therefore, Dreifus et al. concluded that HRV may offer information about sympathetic and parasympathetic autonomic function and could serve as a measure of risk stratification for serious cardiac arrhythmias and possible sudden cardiac death. The most important application of HRV analysis is in its prognostic indication for sudden cardiac death (Futterman & Lember, 1994).

2.4 Clinical Relevance of Autonomic Dysfunction

A balance between the two branches of the ANS is essential for good health. A majority of illnesses and injuries are caused or result from an imbalance in the two branches of the ANS. Any type of dysfunction or imbalance between the two branches of the ANS is referred to as dysautonomia. Dysautonomia may also refer to failure of the ANS. Autonomic imbalance has the potential to influence cardiac events. Cardiac events such as variability in heart rate or blood pressure can be affected by autonomic dysfunction. As a result of changes in HRV, other diseases or events may occur such as heart failure and myocardial infarction. Thus, early subclinical detection of autonomic

dysfunction by measurement of HRV is important for risk stratification and subsequent management (Task Force, 1996).

Autonomic dysfunction is associated with and contributes to the progression of chronic congestive heart failure (CHF). Autonomic dysfunction is an important feature of congestive cardiac failure. Heart failure is a progressive disorder in which damage to the heart causes weakening of the cardiovascular system. It can be clinically manifested by fluid congestion or inadequate blood flow to tissues, which is referred to as myocardial ischemia. Heart failure progresses by inappropriate responses of the body to injury of the heart. It is a complex condition because it may be a result of one or many different causes. For example, cases of untreated long-term hypertension can evolve into development of cardiac failure. Heart failure is a disorder that has to be managed in regard to not only the state of the heart, but the condition of circulation, lungs, neuroendocrine system and other organs.

Eckberg, Drabinsky, and Braunwald (1971) were the first to show that there was defective cardiac parasympathetic control in patients with heart failure. In CHF, activation of several neurohumoral systems, such as the sympathetic nervous system, renin-angiotensin system, and the argininevasopressin system occurs (Soejima et al., 2000). High plasma levels, increased sympathetic nerve activity, resetting of baroreflex control, and parasympathetic withdrawal have been reported in patients affected by this syndrome (Lucreziotti et al., 2000). Soejima et al. concluded that the level of catecholamines, mostly norepinephrine, increases and is correlated with the severity of heart failure. Increased sympathetic activity in CHF has also been well documented by

increased cardiac noradrenaline overflow and muscle sympathetic activity. Thus, CHF is a known condition that may develop over time as a result of dysautonomia.

It has been reported that hypertension has some of the same findings in HRV as those in heart failure. Langewitz, Ruddle, and Schachinger (1994) found reduced parasympathetic function in hypertensive patients. Also, Langewitz et al. (1994) reported hypertension to be characterized by a depressed circadian rhythmicity of LF. Other investigators found hypertensive patients to have increased sympathetic nervous system activity even at rest (Guzzetti et al., 1991). So, hypertension can provide important lessons about the adverse effects of sympathetic predominance (Curtis & O'Keefe, 2002). High blood pressure can be a sign of chronic imbalance of the autonomic nervous system.

Coronary artery disease (CAD) is a risk factor for myocardial infarction (MI). Individuals with MI are at high risk for cardiac mortality and usually have decreased HRV. CAD is a type of cardiovascular disease usually caused by atherosclerosis, a progressive and degenerative arterial condition leading to occlusion of affected blood vessels. This pathology can lead to a reduction in blood flow. Reduced blood flow can eventually affect the balance of the autonomic nervous system. The association of autonomic imbalance with incident cardiovascular disease and all-cause mortality in the general population has been attributed to subclinical coronary artery disease (Gerritsen et al., 2001). Decreased HRV is associated with an adverse prognosis in patients with coronary artery disease (Hayano et al., 2001). While the depression of HRV has been observed in many clinical settings, the clinical implication of HRV analysis has been clearly recognized in only two of these clinical contexts: (1) as a predictor of risk of arrhythmic events or sudden cardiac death after acute MI and (2) as a clinical marker of

evolving diabetic neuropathy (Stys & Stys, 1998). The role of HRV assessment has also been recognized and is still being applied in the evaluation and management of heart failure.

The importance of HRV for the stratification of patients who are at high risk after acute myocardial infarction (AMI) has been well documented (Malik, Farrell, & Camm, 1990). The prognostic value of HRV with respect to survival from and outcome of MI has attracted increasing interest (Moser et al., 1994). Because HRV mirrors autonomic equilibrium, it is not surprising that recent studies revealed prognostic possibilities for HRV measurements following myocardial infarction (Moser et al., 1994).

Dysfunction of the autonomic nervous system is associated with increased risk of mortality in patients with diabetes, survivors of myocardial infarction, and unselected middle-aged elderly subjects (Gerritsen et al., 2001). Gerritsen et al. has explained this by the fact that autonomic imbalance predisposes individuals to cardiac arrhythmias. Subjects with diabetes are known to be at high risk of developing autonomic dysfunction, and autonomic dysfunction is already present in patients with newly diagnosed diabetes (Lehtinen, Uusitupa, Siitonen, & Pyorala, 1989). As a complication of diabetes mellitus, autonomic neuropathy is characterized by early and widespread neuronal degeneration of both sympathetic and parasympathetic tracts of the nervous system (Task Force, 1996). The severity of autonomic neuropathy is marked by the fact that it affects both components of the ANS.

2.5 Heart Rate Variability

HRV is a time series that bears information on instantaneous heart rates or current R-R intervals. Usually, increased HRV reflects increased autonomic modulation of the

heart, and the converse is also true (Stein & Kleiger, 1999). Measures of HRV are increasingly being employed in applications ranging from basic investigations of central regulation of autonomic state, to studies of fundamental links between psychological processes and physiological functions, to evaluations of cognitive development and clinical risk (Berntson et al., 1997).

2.6 Heart Rate Variability Quantified in Frequency

Although, the influence of ANS on HRV was recognized early in this century, only recently have several studies made it clear that the parasympathetic and sympathetic activities influence HRV at different parts of the frequency spectrum (Moser et al., 1994). Mathematical analysis of HRV shows that heart rate is influenced by different frequency components because these components arise as a result of different signaling mechanisms of the heart.

The two branches of the ANS, the PNS and SNS, both play a role in modulating normal activity of the heart. A normal heart rhythm is controlled by membrane processes of the cardiac sinoatrial (SA) node. However, these processes may differ based on which branch of the ANS is playing the dominant role in activation. Heart rate fluctuations may occur as a result of the different signaling mechanisms of the PNS and SNS.

Studies have summarized that cardiac response to vagal (PNS) activity is rapid, while the response to sympathetic activity is slower characterized with a time delay. Spear, Kronhaus, Moore, and Kline (1979) examined heart period responses to sympathetic and parasympathetic activity. Their study demonstrated that a vagal burst had its maximum effect at about 0.5seconds. This response returned to baseline within 1 second and then a slower rebound in direction of decreasing the R-R intervals. The

sympathetic burst or stimulus had no effect for approximately 1 second and the return to baseline occurred within 20 seconds. The maximum decrease in R-R intervals was seen at approximately 4 seconds after the sympathetic burst was initiated. This feature may explain why heart rates remain elevated several seconds after an excitatory stimulus is introduced.

Berger, Saul, and Cohen (1989) and Penaz (1962) found similar impulse response results using frequency-domain techniques. Here, the vagal filter had a corner frequency of 0.15 Hz. Berger et al. (1989) also found that the corner frequency and response characteristics varied slightly as a function of the mean vagal stimulation frequency. The direct current intercept was larger at lower stimulation frequencies and the corner frequency was lower than at higher frequencies. Berger (1987) also examined response of sinus node to modulation of sympathetic nervous system activity. Similar to what was reported by Spear et al. (1979), Berger found the sympathetic response to have a corner frequency of 0.015 Hz. This revealed a time delay of about 1.7 seconds. The studies by Berger (1987) and Spear et al. (1979) found similar results and summarized that vagal responses are faster with little delay, whereas sympathetic responses are slower with a 1-2 seconds time delay.

The differences in the delay of cardiac response to sympathetic and parasympathetic activation appear to be related to the receptor processes and postsynaptic responses (Berntson et al., 1997). Hill-Smith and Purves (1978) determined that the response characteristics were not due to differences in diffusion at muscarinic (vagal) or adrenergic (sympathetic) receptors. This study suggested that the delay in cardiac responses to these neurotransmitters probably arose from processes subsequent to the

binding of the agonist to the receptor (Berntson et al., 1997). In addition, Hille (1992) demonstrated that the linkage between muscarinic receptor activation and ionic current changes is mediated by signaling molecules located within the cell membrane. The parasympathetic neurotransmitter, ACH, is lipid-soluble and able to pass through cell membrane without use of a second-messenger. This may explain why vagal stimulation occurs much quicker and with little time delay than sympathetic stimulation.

Adrenergic (sympathetic) stimulation is initiated in the membrane and requires a second-messenger activation of a protein kinase in the cytosol. This is necessary because the neurotransmitter, NE, is a water-soluble molecule and unable to pass through the cell membrane. The activation of the second-messenger eventually sends a signal back to the membrane to change the ionic currents (Hille, 1992). This activity takes longer than that of vagal activity because of the delay involved in the use of a second-messenger activator rather than direct activation. This feature, as well as the rate of termination of receptor action appear to be responsible for differences in time constants of sympathetic and vagal responses (Levy, Yang, & Wallick, 1993).

Thus, HRV components tend to aggregate within several frequency bands (Berntson et al., 1997). Respiratory frequency band (RSA) is the most conspicuous of the bands. It is considered to range from about 0.15 Hz to 0.4 Hz in humans but may extend below 0.15 Hz and up to 1 Hz or more in infants and adults during exercise (Berntson et al., 1997). This frequency band range is referred to as the high-frequency (HF) band (Task Force, 1996). RSA is generally believed to provide an index of vagal activity, which is characterized by the HF band.

R-R interval oscillations also occur at low frequencies (about 0.05-0.15 Hz). This range is termed the mid-frequency range by some, but is more commonly known as the low-frequency (LF) range. The LF heart rate rhythms have been suggested to reflect mainly sympathetic outflow (Malliani, Pagani, Lombardi, & Cerutti, 1991; Malliani, Pagani, & Lombardi, 1994) but have also been thought to reflect both sympathetic and vagal activity (Akselrod et al., 1985; Pomeranz et al., 1985). Studies have shown the parasympathetic nervous system to be able to modulate heart rate effectively at all frequencies between 0 and 0.5 Hz. These frequencies are higher than that of the sympathetic nervous system. Sympathetic modulation of heart rate occurred with significant gain only at frequencies below 0.1 Hz (Berntson et al., 1997).

Bootsma et al. (1994) summarized LF and HF by reporting LF fluctuations to be mediated by an unknown mixture of sympathetic and vagal influences. Whereas, HF fluctuations are believed to be solely vagally mediated. Furthermore, Bootsma et al. along with other investigators (Malliani et al., 1994; Montano et al., 1994) have proposed that power in the LF and HF reflects the relative balance between sympathetic and vagal control. This is referred to as autonomic or “sympathovagal” balance and can be indexed by the LF/HF ratio (Berntson et al., 1997).

2.7 Heart Rate Variability as a Method of Autonomic Measurement

Studies of the functional effects of phasic modulation of sympathetic and vagal activities are especially pertinent to the patterns of heart rate variability (de Boer, Karemaker, & Strackee, 1985; Somsen, Molenaar, van der Malen, & Jennings, 1991). The previous paragraphs provide insight about the different signaling mechanisms of the heart and how those ideas were developed. This information provides theoretical basis

for HRV being employed as a measure of ANS activity. The developed theories explain why the mechanisms are described in terms of frequency. Furthermore, it is clear why investigators refer to sympathetic activity in terms of LF and parasympathetic as HF. To develop theories to explain the control of the autonomic nervous system, many different studies were performed. Because neither vagal nor sympathetic nerve traffic to the human heart has been measured directly, conclusions regarding the heart rate fluctuations are based on indirect evidence. The following studies have shown HRV to be an effective tool in clinical assessment of ANS control of the heart.

HRV analysis has been employed in several different settings as a means of measuring the autonomic nervous system. For instance, HRV analysis is commonly used to assess the effect of exercise on the autonomic nervous system control of the heart. Some studies have shown that exercise training may confer anticipatory protection from sudden death by enhancing cardiovascular autonomic function (Hull et al., 1994). The data found in this study supports the concept that good aerobic fitness may exert cardioprotective effects by enhancing the cardiac vagal function during exercise.

Another study determined that HRV appears to be a potentially good indicator of cumulated training load in middle-distance runners, which could help to plan training programs (Pichot et al., 2000). This study confirmed that heavy training shifted the cardiac autonomic balance toward a predominance of the sympathetic over the parasympathetic drive. When recorded at night, HRV appeared to be a better tool than resting heart rate to evaluate cumulated physical fatigue. This may be because of the magnification of the induced changes in the ANS activity. These results may be of interest for optimizing training profiles (Pichot et al., 2000).

Perini, Fisher, Veicsteinas, and Pendergrast (2002) examined the effects of an intense aerobic training program on cardiovascular responses at rest and during exercise in older men and women. They also looked at HRV as an expression of autonomic modulation and evaluated subjects over the age of 70 years. Perini et al. (2002) demonstrated that aerobic training increased exercise capacity and decreased blood pressure in the subjects. However, they saw no changes in autonomic regulation of the heart. This particular study suggests that the adaptations to aerobic exercise used in this study were peripheral in nature.

While Perini, Fisher, Veicsteinas, and Pendergrast (2002) found no adjustments in ANS modulation, other studies conclude that physical activity may have an overall positive effect on HRV. Myslivecek, Brown, and Wolfe (2002) examined the effects of physical conditioning on cardiac autonomic function in healthy middle-aged women. The exercise protocol was a 12 week walking program. After training, participants displayed increased vagal modulation and during exercise vagal modulation was higher with lower sympathetic modulation. All the participants improved according to the pre-training values.

HRV has been employed as a measure of autonomic activity in numerous studies examining the effect of posture or tilt on the ANS. Cooke et al. (1999) examined the interactions between autonomic neural oscillations during passive upright tilt. Using fast-fourier transform spectral analysis they found integrated areas of muscle sympathetic bursts and LF powers increased. The increases occurred directly and significantly with the tilt angle. It was concluded that tilt produced sympathetic stimulation increases to a

level that overwhelms the respiratory gate, and vagal stimulation decreases it to a level below that necessary for maximal respiratory gating to occur.

Montano et al. (1994) also investigated the capability of HRV analysis to quantify graded changes in sympathovagal balance induced by passive tilt. The results of this study indicated that use of HRV analysis to assess progression of a sympathetic excitation, of a vagal withdrawal, and consequently, of a shift in sympathovagal balance were indeed efficient. It was confirmed in this study that analysis of HRV can noninvasively quantify changes in sympathovagal balance accompanying graded passive tilt. Bloomfield et al. (1997) examined change in autonomic balance as a result of passive tilt in comparison to actively standing up. Although the initial 30 seconds of standing up showed different changes in R-R intervals, the average changes in R-R interval during the first five minutes of standing are similar to the average changes in R-R interval during the first five minutes of passive tilt. Similar findings were reported in a study by Bahjaoui-Bouhaddi, Henriet, Cappelle, Dumoulin, & Regnard (1998).

Patwardhan, Evans, Bruce, Eckberg, and Knapp (1995) performed a study in which the effect of breathing on vagal modulation was investigated. They specifically examined metronomic breathing to determine whether it complicates the interpretation of heart rate spectra by altering vagal modulation. They compared the metronomic breathing to spontaneous breathing patterns. Their findings showed heart rate power in the respiratory frequency (where vagal modulation occurs) region. The results suggested that vagal modulation of heart rate is not altered and vagal tone is not enhanced during metronomic breathing.

In another study, Bloomfield et al. (2001) questioned the report made by several investigators that the HF band cannot be interpreted unless the breathing rate is controlled. They measured HF power during spontaneous breathing and compared it to HF power during metronome-guided breathing. They found no significant differences between HF power measured during spontaneous and metronome breathing in the group as a whole and when patients and healthy subjects were measured separately. The data obtained indicate that HF power during spontaneous and metronome breathing differs at most by very small amounts. In addition, they found HF power to be relatively constant across the range of typical breathing rates. Bloomfield et al. concluded that there is no need to control breathing rate to interpret HF power when RR variability, specifically HF power, is used to identify high-risk cardiac patients.

Thus, HRV analysis has also been shown to be useful in determining whether breathing patterns affect ANS modulation. Various studies (Bloomfield et al., 2001; Bahjaoui-Bouhaddi, Henriët, Cappelle, Dumoulin, & Regnard, 1998; Pichot et al., 2000; de Boer, Karemaker, & Strackee, 1985; Somsen, Molenaar, van der Malen, & Jennings, 1991) were successful in discovering useful information about ANS control that can be applied in a series of human and animal studies. HRV assessment has been explored as a measure of autonomic activity in relation to effects of exercise or physical activity on the ANS. Also, several studies using tilt or postural changes, as well as breathing patterns have reported the use of HRV analyses as the measure of ANS activity.

In summary, many studies have shown that whenever the signal produced by HRV was adequate and the sympathovagal balance was shifted toward a sympathetic predominance with tilt, moderate hypotension (Rimoldi et al., 1990) mild physical

exercise, mental stress (Pagani et al., 1991) or coronary artery occlusion (Rimoldi et al., 1990) the LF or LF/HF component was augmented (Montano et al., 1994). This suggests that various conditions do affect the modulation of the heart by the autonomic nervous system and have validated the use of HRV as a measurement of autonomic activity.

Clearly, HRV represents one of the most promising quantitative markers of autonomic activity. The easy derivation of this measure has popularized its use. As many commercial devices now provide an automated measurement of HRV, professionals have been provided with a seemingly simple tool for both research and clinical studies (Task Force, 1996). Patterns of HRV hold considerable promise for clarifying issues in physiology (Berntson et al., 1997).

2.8 Types of Heart Rate Variability Analysis

There are two basic approaches to quantifying HRV (a) the use of global descriptive statistics to characterize the distribution of heart periods (e.g., range, standard deviation, and variance) and (b) modeling of periodic patterns to extract specific frequency components of variance that relate to functional processes or physiological mechanisms (Berntson, et al., 1997). The variations in heart rate may be evaluated by a number of methods. There are two approaches to the measurement of HRV: analysis in the time or in the frequency domain. Perhaps the simplest to perform are the time domain measures, in which either the heart rate at any point in time or the intervals between successive normal complexes are determined (Task Force, 1996).

Time and frequency domain analysis are both types of spectral methods used to analyze HRV. Simple time domain measures can then be calculated such as, the mean NN (R-R) interval, the mean heart rate, the difference between the longest and the

shortest NN interval, and so forth. There are two classes of time domain variables, one based on interbeat intervals and the other based on comparisons of the lengths of adjacent cycles (Stein, Bosner, Kleiger, & Conger, 1994). Those based on interbeat intervals include the standard deviation of all normal R-R intervals (SDNN), and the standard deviation of the mean of 5-minute intervals, averaged over a 24-hour period (SDANN). The HRV triangular index is also an estimate of overall HRV.

The second class of time domain variables based on comparisons of length adjacent cycles includes the proportion of adjacent cycles that are >50 milliseconds apart measured in percent (pNN50), and the root mean square successive differences (r-MSSD), which is the square root of the averaged sum of squared differences in length between all adjacent NN cycles (1994). Other time domain measurements that can be used are variations in instantaneous heart rate secondary to respiration, tilt, Valsalva maneuver, or phenylephrine infusion (Task Force, 1996).

Various spectral methods for the analysis of the tachogram have been applied since the late 1960s (Task Force, 1996). Power spectral density (PSD) analysis provides the basic information of how power (variance) distributes as a function of frequency. Analysis in the frequency domain is mathematically more complex, but has been used by a number of investigators (Stein, Bosner, Kleiger, & Conger, 1994). Stein et al. (1994) concluded that frequency domain analysis yields information about the amount of the overall variance in heart rate resulting from periodic oscillations of heart rate at various frequencies. Investigation of the underlying rhythms is what is addressed using the frequency domain analysis.

2.9 Fast Fourier Transform

Fast Fourier transform (FFT) is one of the most common approaches to spectral analysis of HRV. The majority of studies on cardiovascular signals have been performed using a FFT (Lotric, Stefanovska, Stajer, & Rovan, 2000). FFT is a type of spectral analysis that produces a decomposition of total variation of a data series into frequency components. The FFT can produce frequency- and time-domain indices, but is considered a frequency-domain method of HRV analysis. The FFT approach could be considered a descriptive method and captures the data in either the time-or frequency-domain separately—not simultaneously. Although several types of analyses are employed in HRV studies, the FFT is the form of spectral analysis examined in this particular study.

2.10 Limitations of Fast Fourier Transform

FFT assumes that the time series contains only deterministic components and that the data are stationary signals (Berntson et al., 1997). FFT-based techniques include all data as oppose to the Autoregressive (AR) modeling, another form of spectral analysis, which excludes “noise.” FFT, being a form of frequency-domain analysis, suffers from several drawbacks. For example, it fails to provide time localization of signal singularities characterized by high-frequency components (Gramatikov & Georgiev, 1995). Because of the low-amplitude windows produced by FFT, the most interesting part of the QRS segment of the ECG is often masked out. This results in the possibility of overlooking late potentials in the ECG. Late potentials are regarded as a manifestation of delayed electrical conduction or reentry mechanism in the heart. Their diagnostic prevalence has been discussed extensively (Berbari & Lazzara, 1992; Breithardt et al.,

1982; Zimmerman, Adamec, Simonin, & Richez, 1985) and inability to detect them may result in misdiagnoses.

Another problem posed by the FFT, is the difficulty to detect a given frequency. This is complex because in order to detect a frequency, the signal must be observed for at least one period of a particular frequency. Then, it is impossible to say exactly at which time the signal had the particular frequency (Lotric et al., 2000). Another limitation of the FFT is the resolution and its inadequacy in producing peaks at low frequencies. A peak falling between frequencies that cannot be picked up by the FFT is undetected. Moreover, this peak may contribute to all frequencies in the spectrum. FFT also assumes that ECG signals are stationary in nature. This however, is not always the case.

2.11 Discrete-Wavelet Transform

The other form of HRV analysis in question in this particular study is the discrete wavelet transform (DWT). The recently introduced wavelet transform is a member of the class of time-frequency representations, which include the Gabor short-time Fourier transform and Wigner-Ville distribution. In essence, a wavelet decomposition of a signal amounts to its description in terms of shifted and dilated versions of some basis wavelet. The shift operation allows signals to be localized in time, while the dilation operation enables the scale of the original signal to be determined. Hence, a signal can be localized in both time and scale (which can be considered as similar to frequency) dimensions thus leading to the term “time-scale” representation (Crowe, Gibson, Woolfson, & Somekh, 1992). Wavelets were introduced by Grossman and Morlet in 1984. The method is based on the multiresolution signal decomposition (Bartnik, Blinowska, & Durka, 1992).

The wavelet techniques are of significance because of their ability to display the spectral content of a signal as time elapses (Crowe et al., 1992).

The value of the wavelet transform as a signal analysis tool has been demonstrated by its successful use in studying turbulence and processing of speech and music. It has also been used for geophysics investigations and fractal analysis. Bartnik, Blinowska, and Durka (1992) introduced wavelet formalism for the first time to brain signal analysis. Akin (2002) compared wavelet transform to FFT methods in the analysis of EEG signals and found WT to be a better method for detecting brain diseases.

2.12 Advantages of Wavelet Transform

DWT is a mathematical recipe that can be compared to FFT in respect to orthogonality and invertibility (Ashkenazy et al., 1998). However, unlike the FFT, the logarithmic frequency resolution of the wavelet analysis makes it possible for this method to capture simultaneously very different rhythms within a single signal (Lotric et al., 2000).

Also, wavelet estimation is calculated directly from data, and no modeling is involved as in the case of linear modeling. Wavelet frequency resolution of the wavelet transform enabled the detection of peaks in very low frequency intervals instead of masking out important parts of ECG data (Lotric et al., 2000). The wavelets are unit vectors that correspond to sine and cosine basis functions of the FFT. They decompose data sets more intrinsically, in turn, rendering functions with inaccuracies into more reliable data than that of FFT (Ashkenazy et al., 1998).

Wavelet transform has better time resolution at higher scales than that of FFT. This is directly related to the sampling patterns of the discrete transforms in phase-space.

Therefore, the wavelet transform has the ability to localize singularities more accurately in the time domain. Also, there is near perfect reconstruction from the transform coefficients without the requirement for oversampling (Crowe et al., 1992). Ashkenazy et al. (1998) established that large classes of biological data such as ECG series and R-R intervals may analyzed by DWT.

2.13 Summary

Measures of HRV may offer powerful tools for clarification of relationships between psychological and physiological processes. However, there are caveats and pitfalls in the measurement, analysis, and interpretation of HRV (Berntson et al., 1997). The significance of and meaning of the many different measures of HRV are more complex than generally appreciated, and there is potential for incorrect conclusions and for excessive or unfounded extrapolations (Task Force, 1996). There are other limitations associated with the model of HRV most commonly used in clinical settings up to date (FFT). With this being the case, it is possible that assessment of HRV would benefit from other approaches such as wavelet transformation. Therefore, the purpose of this study is to examine the extent to which the traditional approach to spectral analysis of HRV can discriminate between healthy and diseased populations in comparison to wavelet analysis.

CHAPTER 3—METHODS

3.1 Participants

Seven (1 male, 6 females) class II and III CHF patients and eight (4 males, 4 females) volunteer control subjects were recruited to participate in this study. The CHF patients were classified according to the New York Heart Association Heart Failure Classifications (Table 3.1). The groups were matched according to age (mean \pm standard deviation; CHF: 51.9 \pm 17.6 yrs; Control: 49.5 \pm 17.9 yrs). Individuals recovering from recent hospitalization, with unstable myocardial ischemia and/or angina, uncontrolled diabetes mellitus and/or hypertension were excluded from this study. Those with lung disease, anemia, or renal failure were also prohibited from participation in this study. All patients were still taking their physician prescribed medications during the data collection for this study. The medications included beta-blockers, calcium-channel blockers, diuretics, anti-coagulants, lipid-lowering agents, anti-anginal agents, ACE inhibitors, and digitalis drugs. Additional medications taken by some of the participants included: anti-anxiety agents, and hormone replacement therapy.

Table 3.1-New York Heart Association: Heart Failure Classifications

Classification	Symptoms
Class I	None
Class II	Mild symptoms and slight limitation during normal physical activity. Comfortable at rest.
Class III	Marked limitation in activity due to symptoms, even during limited activity. Comfortable only at rest.
Class IV	Severe limitations of activity and symptoms at rest.

3.2 Medical History and Consent Forms

Every participant gave a self-report of his/her medical history (medications, hospitalization, surgeries, falls etc.) and tobacco history (smoker, non-smoker, tobacco type, number of years as a smoker, etc.) Each participant received a comprehensive explanation of the study. The explanation included instructions, benefits, and inherent risks, as well as expected commitments. Following the explanation, all participants signed an informed consent approved by the Institutional Review Board of Louisiana State University.

3.3 Experimental Procedure

All measurements were performed on each subject in a quiet examination room. Each participant rested on an examination table in supine position and allowed fifteen minutes to adapt to the testing environment before measurements were obtained. For the purpose of this study, the following stages of measurement were focused on (1) supine position with spontaneous breathing (SB) for five minutes (2) supine position with paced breathing (PB) for five minutes. SB is the term used to refer to the normal breathing pattern, while PB consists of one breath every 5 seconds. Each breath consisted of an inhalation and exhalation each lasting 2.5 seconds in duration. A blood pressure cuff was placed on the left arm of the participant and blood pressures were taken automatically during testing. During each stage, heart rate and blood pressure measurements were obtained. The event marker on the Biopac System was used to mark the beginning and end of each stage in the protocol.

In addition, each participant performed a six-minute walk test. The total distance each participant walked was recorded in meters. Their HR, BP, and RPE were recorded as well.

3.4 Data Reduction and Analysis

The electrocardiogram signal was captured by the Biopac System and digitized using Acknowledge computer software. Three-lead electrocardiogram signals were transformed into tachograms by the Acknowledge software, and resampled at 4 Hz. The tachograms were then analyzed for the standard deviation of all normal R-R intervals (SDNN). The tachogram was then subjected to a FFT and the resultant power spectrum was examined for LF, HF, and LF/HF ratios. All the data were subjected to analysis using the Matlab version 6.3 software. HF power is a pure parasympathetic signal modulated by respiration (Pomeranz, et al., 1985). LF is modulated by baroreflex activity and provides information about both sympathetic and parasympathetic modulation of R-R intervals. The ratio of LF power to HF power will be calculated as an index of autonomic balance. The data were also submitted to the Daubechies-4tap discrete wavelet transformation (DWT). This transformation computes coefficients (or powers) that are occurring at different levels of frequency. In the case of 256 intervals the Daubechies 4-tap computes 7 different levels (1-7) corresponding to events cycling every 2, 4, 8, 16, 32, 64, and 128 intervals beats, respectively. The frequency that the level relates to is also a function of the length of the average R-R interval. Typically however, events cycling every 16-32 intervals are relatively low in frequency of occurrence, whereas events cycling every 4 or 8 intervals are typically representing HF oscillations. After computing the coefficients at all 7 levels, the MATLAB script was

written so as to pick out the levels describing LF oscillations, sum the coefficients, and then divide by the sum of the coefficients of the levels describing HF oscillations. This ratio was used as wavelet derived low-to-high frequency ratio of sympathovagal balance.

3.5 Statistical Analysis

All statistical analyses were performed using SPSS statistical software. The data were expressed in mean and standard deviation. A mixed-model analysis of variance (ANOVA) was employed to examine the main effects of group (CHF vs. control) and breathing condition (SB and PB), as well as, group by breathing condition interactions. T-tests were used to examine possible differences between the SB and PB conditions within both groups. The t-tests were also used to examine the differences in participant characteristics (height, weight, BMI, and age) between the two groups. For the statistical analyses, alpha was set a-priori at 0.05. The R-R intervals were examined along with the SDNN, HF, LF, pNN50, RMSSD, and LF/HF ratio of the R-R intervals. The LF/HF ratio data were collected from the FFT and wavelet analysis. These data were plotted in order to visualize differences between the FFT and the wavelet data. Finally, we used Pearson correlation coefficient to report the wavelet derived LF/HF ratios during SB and PB for any correlation with the six-minute walk distance and BMI of each participant.

CHAPTER 4—RESULTS

Fifteen individuals participated in this study. Seven of them had been diagnosed with the condition of heart failure and the others were volunteers without any type of cardiovascular disease and served as the control group. There were no differences in CHF and Control group participant characteristics as described below in Table 4.1.

Table 4.1- Participant Characteristics

Characteristics	CHF	Control
n	7	8
Age (yrs)*	51.9 +/- 17.6	49.5 +/- 17.9
Height (cm)*	164.5 +/- 5.5	172.9 +/- 11.4
Weight (kg)*	98.3 +/- 25.6	78.7 +/- 12.9
Gender	1 male, 6 females	4 males, 4 females

*Values are mean +/- standard deviation

A number of acronyms will be used throughout the results chapter. For reference purposes, the following table (Table 4.2) presents these acronyms and their corresponding definitions.

Table 4.2-Acronyms

Variable	Definition
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
HR	Heart Rate
SB	Spontaneous Breathing
PB	Paced Breathing

Table 4.2 continued on next page

LF	Low Frequency
HF	High Frequency
SDNN	Standard Deviation of all NN intervals
LF/HF	Measure of sympathovagal balance, reflection of sympathetic modulations
RMSSD	The square root of mean of sum of squares of differences between adjacent NN intervals
NN50	Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire ECG recording
pNN50	NN50 count divided by total number of all NN intervals
nu	Normalized units
BMI	Body Mass Index

Table 4.3-Blood Pressure and Heart Rate Responses

Breathing Condition	CHF		Control	
	SB	PB	SB	PB
SBP	136 +/- 16.6	133 +/- 16.9 †	128.2 +/- 15.7	125.7 +/- 15.7 †
DBP	82 +/- 11.9	81.8 +/- 13.6 †	71.2 +/- 7.96	72.5 +/- 4.2 †
HR	78.7 +/- 11.9	77.6 +/- 11.3 ††	61.7 +/- 5.0	62.5 +/- 8.5 ††

Acronyms found in Table 4.2

† Significantly ($p < 0.05$) different from SB

†† Group x condition interaction ($p < 0.05$)

Values are mean +/- standard deviation

4.1 Heart Rate and Blood Pressure

Table 4.3 shows the SBP, DBP, and HR responses measured during data collection. There were several main effects of the breathing condition. HR and BP measures during PB were different from those observed during the SB stage. The main effect on HR; however, was modified by a group by condition interaction. There was

only one main effect of group. The HR decreased from the SB stage to PB in the CHF and increased from SB to PB in the control group.

4.2 CHF vs. Control: Fast Fourier Transform

Table 4.4 shows the mean scores for HRV components following analysis using the FFT method. There was only one significant difference between the CHF and control group using FFT. This difference was a main effect of group on the R-R intervals. The R-R intervals were greater in the control as compared to CHF group. The R-R intervals during both the SB and PB ($p=0.001$, $p=0.022$, respectively) were different between groups.

4.3 CHF vs. Control: Discrete-Wavelet Transform

The values for the derived wavelet LF/HF ratio are listed in Table 4.4. There was a group by condition interaction on the wavelet LF/HF ratio ($p=0.024$) between groups in the SB stage. This was such that the LF/HF ratio was higher in the control group as compared to the CHF group.

4.4 Breathing Condition Effects

A mixed model ANOVA and then paired t-tests were used to examine differences between breathing conditions within both the CHF and control group. Table 4.3 shows the values (\dagger) in which there were several significant differences between the SB and PB stages. The values shown were obtained as a result of the FFT method. The SDNN values were higher during PB as compared to the SB stage. There was a difference found between the two stages ($p<0.05$), but there were no interactions between the control and CHF group. The R-R intervals were different ($p<0.01$) between the PB and the SB stage being that they were lower during the PB stage. As mentioned in the previous section,

there was also a difference between groups in the R-R intervals. The R-R intervals were higher in the control group. The LFnu values significantly lower in the PB ($p<0.01$) as compared to the SB stage. Although the values for the control group were higher than that of the CHF group, the LFnu values between the groups were not significantly different. The HFnu values were significantly different between the SB and PB conditions. This was such that the HFnu values were greater ($p<0.01$) during the PB stage. There were no differences detected in HFnu values between the groups. Overall, the values for the pNN50 parameter were smaller in the CHF group than that of the control group. However, there were no significant differences between the groups. The differences were detected during the breathing stages. The pNN50 values during PB were lower during the SB stage, and there was a significant difference ($p<0.01$) between the two breathing conditions. The CHF group showed greater values in RMSSD than that of the control group, but the values were not found to be significantly different. The RMSSD values were different ($p<0.01$) between the two stages. The RMSSD was higher during the PB stage than it was during SB. Lastly, the LF/HF ratio was significantly different between the PB and SB stages. The LF/HF ratio in the PB was found to be smaller than that of the SB stage ($p<0.01$). The wavelet technique detected no differences between the SB and PB conditions in the derived LF/HF ratio.

4.5 Wavelet Powers for CHF and Control Groups

In Figures 4.1 and 4.2 each wavelet power level is plotted for participants of both groups. The power levels on the x-axis reflect frequency (HF and LF). As the power levels increase, the frequency level decreases. In this study, the levels 3 and 4 roughly represent the parasympathetic (HF) activity while levels 5 and 6 represent the

Table 4.4-Wavelet and FFT Values

	CHF		Control	
Breathing Condition	SB	PB	SB	PB
SDNN	51.2±47	61±38.4†	52.5±11.4	59.4±19.4†
R-R	755±81.3	745±95.5†	1002±98*	926±134*†
LFnu	46.9±25	31±15†	62.1±21.2	43±29.8†
HFnu	53.3±25	69±15.3†	37.9±21.3	56.8±29.7†
LF/HF	1.6±1.9	.503±.40†	2.42±1.9	1.67±2.1†
pNN50	15.3±23.2	17.8±22.4†	25±21	23.1±22.5†
RMSSD	57.2±73.4	71.1±59.7†	45.3±28	45.9±28.6†
Wavelet ratio	3.39±.75	3.44±.942	4.41±.43*	4.04±.86*

Acronyms are defined in Table 4.2

* Different from CHF (p<0.05)

† Different from SB condition (p<0.05)

Values are mean +/- standard deviation

area of sympathetic (LF) activity. The y-axis represents coefficients or the standard deviation for the wavelet powers. Figure 4.1 shows the wavelets for the data collected during the SB portion of testing and Figure 4.2 shows the data collected during PB.

4.6 FFT Values for LF in Normalized Units

Figure 4.3 shows the LFnu values obtained via the FFT. The sympathetic activity represented by LFnu is plotted for both the CHF and control groups. The LFnu is the absolute LF power measured in normalized units. The LF normalized units (LFnu) represents the relative value of the LF power component in proportion to the total power (Malliani, Pagani, Lombardi, & Cerutti, 1991). These values were plotted in order to

Wavelet Powers During SB

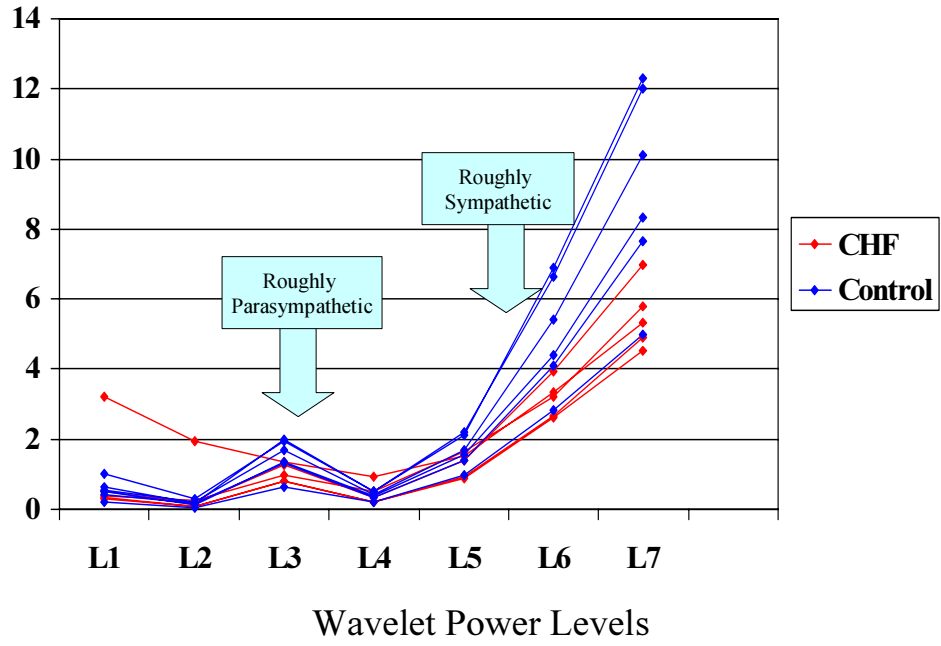


Figure 4.1-Wavelet Powers During SB

Wavelet Powers During PB

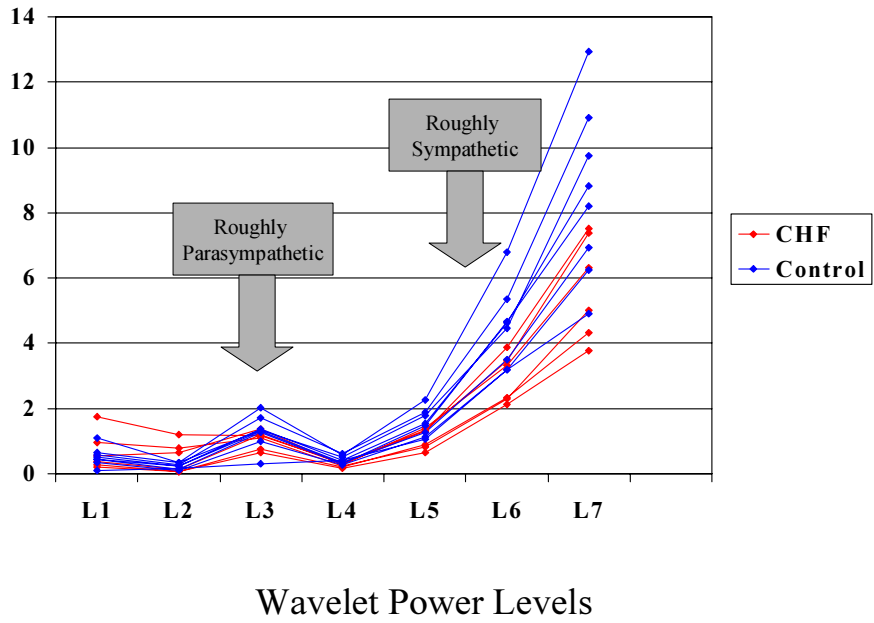


Figure 4.2-Wavelet Powers During PB

visualize a “region of overlap” that occurred following the FFT analysis. It is important here to note that only LF powers were focused on because this is where separation was seen using the wavelet technique. Since we are comparing the two methods, we looked at the ability of the FFT to do what the wavelet has done in terms of separating the CHF and control groups.

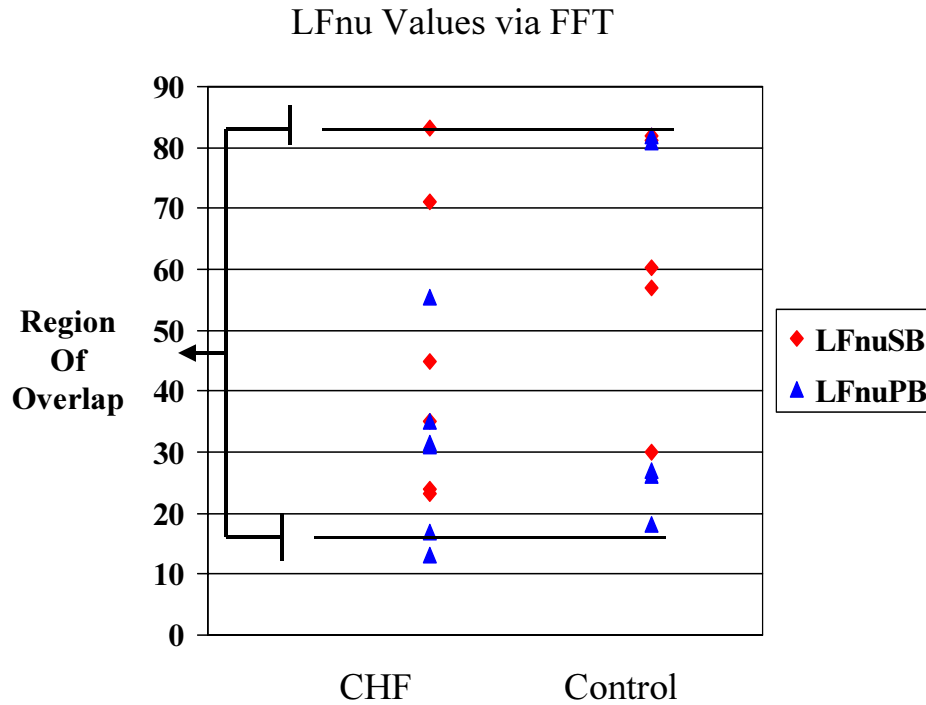


Figure 4.3-LFnu Values via FFT

4.7 Six-Minute Walk and BMI

The means for BMI and six minute walk distances for the CHF and control are listed in Table 4.5. The group means were figured for both the CHF and control groups as a whole. It is important to note that the BMI and walk distances were examined for correlations with the derived wavelet ratios during SB and PB. Also note that the sample size (N) is different than the sample size listed in Table 4.1. There was no correlation found between BMI and wavelet derived ratios during SB or PB. However, there was a

positive correlation (Pearson $r=0.648$) between the group mean walk distance and wavelet ratios during SB. The correlation was found to be significant ($p<0.01$). There was no such correlation between the walk distances and wavelet ratios during the PB stage ($p=0.08$).

Table 4.5-Six-Minute Walk and BMI

	All Participants
N	13
6 Min Walk Distance (m)*	354.7 +/- 194.8
BMI (kg/m²)*	31.3 +/- 11.1

*Values are mean +/- standard deviation

CHAPTER 5—DISCUSSION

The primary purpose of this investigation was to examine the extent to which FFT, a common type of spectral analysis, and the newly introduced discrete wavelet transformation (DWT) could discriminate between a group of CHF patients and age-matched controls. Due to the potential for the test condition to exert considerable influence on HRV, data were collected under spontaneous and paced breathing conditions (SB and PB, respectively). The heart rates and blood pressures of the participants were also examined during data collection.

In general, the observed results appear to be as expected. Our results were similar to those of Ashkenazy et al. (1998). In reference to HRV profiles, the wavelet showed (Figure 4.1 and 4.2) almost complete separation between the control group and the CHF group. The results were similar to Ashkenazy et al. in the fact that any separation was seen. However, our results differed from the Ashkenazy et al. study because the separation was only seen during the sympathetic activity (L5-L6) region. Although it was more distinct in the SB stage, there was separation seen in both the PB and SB conditions. The values for the control group were higher overall in the parasympathetic (L3-L4) and sympathetic regions. The values also increased in greater magnitudes from level 1 to level 7 in the control group, revealing a greater overall LF and HF variation in the control group. By the wavelet data, one could conclude that the control participants had greater parasympathetic- and sympathetic-mediated HRV. The main finding is that DWT analysis appeared to have a greater ability to discriminate between the control and CHF group.

5.1 Heart Rate and Blood Pressure

In this study we also examined HR and blood pressures of the participants in each group. These variables were examined to provide further insight into how the two groups differed during data collection. As expected, the mean blood pressures and resting heart rates were higher in the CHF group. Still, there were no significant differences in SBP or DBP according to group. This may be explained by the fact that CHF individuals were taking medication to control high blood pressure. In addition, high blood pressures (< 140/90 mmHg) were recorded for two of the control participants.

The HR, SBP, and DBP during SB were significantly different from those during PB. However, the influence of breathing on the HR was different between the CHF and control group. In the CHF group, HR decreased from the SB to PB stage. Then, in the control group the HR increased from SB to PB. Thus, it seems guided breathing caused the heart to beat slightly faster in the control group while it slowed the heart in the CHF group. These results also suggest that there was no difference in the way the two groups responded to influence of breathing on the SBP or DBP. Thus, HR seemed to respond differently between the groups as a result of breathing while blood pressures in both groups had similar responses to the breathing conditions.

5.2 FFT Analysis

The LFnu values for both groups obtained by FFT method were also plotted in part because LF (sympathetic) has a tendency to be more pronounced in CHF patients even at rest (Task Force, 1996). There was no distinct separation shown between the two groups. Thus, it is indicated that the FFT lacks the ability that the wavelet had to discriminate between the CHF and control group. Figure 4.3 visually illustrates the

inability of the FFT to discriminate between the CHF and control group. These data are consistent with the findings of Berbari and Lazzara (1992), Breithardt et al. (1982), and Zimmerman, Adamec, Simonin, and Richez (1985). These investigators have shown overlap to suggest that the FFT is inefficient in detecting lower frequencies. The lower frequencies are typically where most late potentials or disturbances in ECG rhythms are found. Late potentials have been shown to be predictive of rhythm disturbances such as sustained ventricular tachycardia (Zimmerman et al., 1985). Thus, the inability to detect them can lead to misdiagnoses and be detrimental in a clinical setting.

The R-R interval is the time duration between each consecutive R wave in an ECG. HRV is the term used to describe variations of these R-R intervals. The data shows the control group to display greater overall variability in R-R intervals than the CHF group. Here, the difference between groups was detected by the FFT. This information is consistent with the findings of Stein and Kleiger (1999), who reasoned that an increased HRV reflects increased autonomic modulation of the heart. Increased autonomic modulation in comparison to a diminished autonomic modulation of the heart usually exists in an individual without cardiovascular disease.

The effects of the breathing conditions on the two groups were also examined in this study. The FFT method was able to detect differences between the SB and PB conditions. The differences were detected in all of the HRV parameters (LF, HF, SDNN, R-R, etc.). This indicates that the HRV analyzed by FFT is affected by breathing patterns, while the HRV analyzed by the wavelet technique is not. However, the ability of the FFT to recognize breathing pattern differences may pose as an advantage in some cases. In studies where breathing patterns are the primary concern or various breathing

patterns are being examined, FFT may be a more powerful tool than the wavelet. Such studies may include those examining the cause of sleep apnea. It is also possible that breathing patterns interfere with accuracy of the HRV analysis if the method of HRV analysis is affected by it. In this case, the wavelet technique may prove a more reliable choice of analysis.

The ability of the FFT to detect breathing differences without showing any separation between the groups may be a result of underlying physiological phenomenon as well as a function of the limitations imposed by the assumption of the FFT.

5.3 Wavelet Analysis

The index of sympathovagal balance (LF/HF) was examined by both the FFT and wavelet techniques. The LF/HF ratio is considered a measure of sympathovagal or autonomic balance and reflects sympathetic modulations. Both techniques showed the control group to have higher LF/HF values than the CHF group. However, only the wavelet detected a significant difference ($p=0.024$) in the LF/HF ratio between the CHF and control group. This difference was detected during the SB stage. Figures 4.1 and 4.2 illustrate the separation that the wavelet detected between the CHF and control group. The illustrations allow one to visualize the greater separation between the groups seen in the SB condition (Figure 4.1).

The higher values in the control group are similar to the findings of Ashkenazy et al. (1998). However, our results differed from Ashkenazy et al. because the separation between groups became more evident in the LF power, meaning only the LF values were higher in the control group. Whereas, the data from Ashkenazy et al. showed higher values and thus separation between groups in both HF and LF powers. The DWT used

by Ashkenazy et al. was the Daubechies 10-tap model. For this investigation, the Daubechies 4-tap DWT was employed. It was concluded by Ashkenazy et al. (1998) that in order to obtain a complete separation between healthy subjects and patients a range of scales, instead of just one, has to be considered. Perhaps, the Daubechies 10-tap filter is closer to the ideal frequency response than the 4-tap. This may also explain the more distinct separation seen by Ashkenazy et al. Equally likely, however, is the possibility that the clinical status of the control group may have involved “silent” disease or other confounding factors such as variation in the fitness levels of the participants.

Regardless, the 4-tap DWT employed here, demonstrated greater discriminatory ability than the FFT in this particular study. This may be explained by the tendency of the FFT analysis to make certain assumptions about ECG data that the wavelet does not. The FFT assumes that the ECG data are stationary signals and that the ECG signal is a continuous time series. The FFT can only accurately describe an event in either the frequency or time domain. Unlike the wavelet, it cannot describe an event in both the time and frequency domain simultaneously. The ability of the wavelet to do this allows a multi-resolution analysis of data with different behavior on different scales. This dual localization renders functions with intrinsic inaccuracies into reliable data when they are transformed into the wavelet domain (Ashkenazy et al., 1998). Furthermore, spectral analyses such as FFT often include transients caused by artifacts, ectopic beats, and noise. All of which possess the potential to impact the power spectrum. This can limit the sensitivity of the FFT technique considerably, and in turn limit its overall applicability.

5.4 Limitations

Overall, the limitations of this particular study evolved around some aspect of the subject population tested. The control group may not have been extremely well matched to the CHF group. The individuals were not matched based on gender, ethnicity or geographical location and there were more females than males in this study. All of these factors have been shown to be influential. In addition, the medications that the CHF individuals were taking may have impacted the results. Thus, it should be stated that the external validity of this study might have been limited in accordance to these factors.

Based on the positive correlation between derived wavelet ratios and the walk distances (Figure 5.1), it is possible that the participant cardiovascular fitness levels influenced the data. This poses another limitation to our data in regard to what was being detected by the wavelet technique. Perhaps this is why there was separation found between the groups during the SB stage. It is possible that the wavelet was detecting the separation based on the fitness variable as opposed to disease. It is also possible that disease is influencing the fitness levels, which in turn are being detected by the wavelet. However, this is only speculation and should be further investigated to provide more insight as to what the wavelet is detecting.

5.5 Future Directions

While this study and similar investigations attempt to develop the most effective tool of HRV analysis possible, other studies should concentrate on examining treatment strategies. For the Kinesiologist, one primary focus should be on physical activity as a form of treatment for those who experience autonomic dysfunction. Some studies have

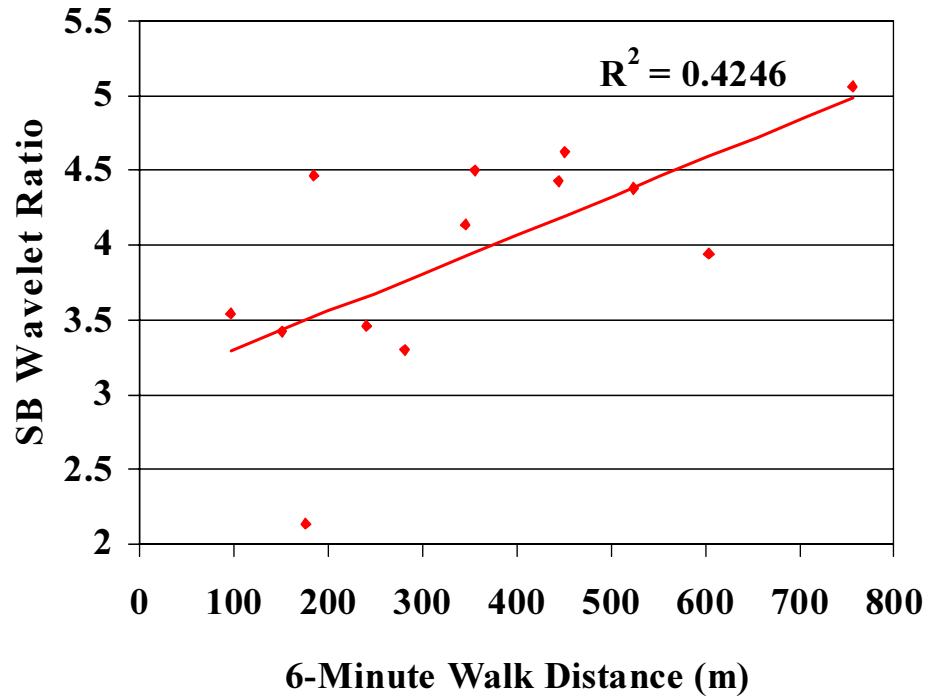


Figure 5.1-6-Minute Walk vs. SB Wavelet Ratio

looked at the effects of physical conditioning on autonomic function. Myslivecek, Brown, and Wolfe (2002) found vagal modulation was higher and sympathetic modulation was lower in exercise groups compared to pre-training values. Also, vagal modulation is increased following moderate intensity aerobic conditioning in middle-aged women (Myslivecek et al., 2002). Another study (Perini, Fisher, Veicsteinas, & Pendergrast, 2002) revealed aerobic exercise training to improve exercise capacity, but failed to demonstrate changes in autonomic regulation of the heart in elderly (70-80 yrs) men and women. Another study by Melanson and Freedson (2001) concluded that a moderate-to-vigorous-intensity exercise program produces increases in time- and frequency-domain measures of HRV within 12 weeks. With findings of this nature, it is important to further investigate physical activity and its effects on autonomic regulation in aims to discover overall effective treatment strategies for dysautonomia.

In addition, there is a need for studies to develop normative data relating wavelet scoring of HRV to cardiovascular risk. Whether the risk of cardiovascular disease varies depending on race, gender, body composition, or geographical location has not yet been established. Also, investigations should report construct validity of the DWT of HRV during exercise, tilt, and mental stress.

5.6 Summary and Conclusions

The purpose of this investigation was inspired by the desire to determine the most efficient method for analyzing HRV. The HRV analysis is an accepted and common method by which the ANS is monitored. It has been established by previous studies that ANS monitoring is of importance for the purpose of enhancing risk stratification and treatment for cardiac diseased populations.

The results support our hypothesis that the wavelet technique would be a more powerful tool for discriminating between the cardiac diseased and control group participants. The data suggested that the control participants had greater overall variability and the magnitude of LF and HF variation was greatest in this group as well. Also, the wavelet seemed to be unaffected by breathing patterns. However, the FFT was able to detect differences in groups as a result of breathing pattern. It is apparent that both the FFT and wavelet provide unique information about autonomic modulation of the heart. Therefore, further research should aim to develop the most effective tools for HRV analysis. HRV studies should also enhance the understanding of physiological phenomena, actions of medications, and disease mechanisms (Task Force, 1996).

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