CHAPTER 1

INTRODUCTION

1.1 Objective

This research sought to understand how autonomic function changes as a result of disease. The systems investigated are influence by the autonomic nervous system. This chapter will discuss the systems under investigation, and the physiological background of the methods developed and described in chapter three.

This research seeks to clarify cardiac autonomic response in disease and aging by developing new statistical methods. These methods are validated in three ways. First, a model was created to simulate the IIBI signal as a summation of cardiac and respiratory oscillatory signals to test the separation technique at frequencies in the cardiac autonomic range. Once the method is verified in this way, it is applied to clinical data sets in an effort to understand the central autonomic changes in cardio-pulmonary interactions. The first clinical application of the methods was a data set consisting of ECG and respiration signals, for COPD subjects and controls. This application evaluated the *central* autonomic influence of pulmonary changes in disease. The next application was in the analysis of the cardiac autonomic response of a subject population with varying levels of visual adaptability, as measured from their ability to adapt to the use of progressive lenses for a condition called presbyopia. This application evaluated the *peripheral* autonomic influence over the oculomotor system, and how it changes with aging, and combined it with the *central* autonomic influence over heart rate variability to determine how, if at all, the two systems interacted.

There are two signal processing approaches taken in this research. The first aids in the classification of the level of health of Chronic Obstructive Pulmonary Disease patients clinically by the use of information contained within the IIBI signal. This method is a non-linear dynamics approach to quantifying variability via an entropy analysis at each scale in a wavelet analysis, and using that information in a k-means cluster separation. The second enables the assessment of cardiac autonomic response with the influence of the respiration, which confounds the analysis of the underlying neural control patterns, removed. The method is a wavelet based statistical source separation technique that employs the correlation between the respiration and IIBI signals at various frequencies to remove the influence of the respiration from the dynamic cardio-pulmonary signal. The foundation for the development of these methods will be discussed in more detail in Section 2.2.

1.2 Hypotheses

There are three hypotheses being tested in this research. The first is that the central autonomic influence over heart rate variability, as evidenced in cardio-pulmonary interactions, is modulated in pulmonary disease. It was hypothesized that lower levels of entropy and cardiac autonomic markers exist in the COPD population than in the control population.

The second hypothesis is that the peripheral autonomic influence over the visual system is linked to the central autonomic influence over cardio-pulmonary interactions. It was further hypothesized that changes in near vision that occur with age are not due solely to lens crystallization and weakening of the muscles. It was also hypothesized that

lowered visual adaptability would be linked with lowered heart rate variability.

The third hypothesis is that the validation of the first two theories would be facilitated by the development of methods that are based upon wavelet transforms. The third hypothesis consists of the development of two specific tools to aid in the analysis of the data sets described above. This hypothesis consists of two parts:

1) The difference in cardio-pulmonary activity between subject populations may be evidenced in the energy of the heart rate signal at different frequencies, which should be distributed differently for people with different levels of health. Further, this difference in energy can be employed to classify the level of cardio-pulmonary health in a clinical setting. Specifically, the development of a wavelet entropy analysis, coupled with the application of a k-means clustering algorithm, will aid in the computer based diagnosis of level of health in COPD. This method will be referred to as the Wavelet Entropy method.

2) Respiration artifact can be successfully removed from a dynamically changing heart rate variability signal to reveal the cardiac changes that occur with aging and disease. This separation can take place in the frequency domain by employing the correlation of coefficient sets generated by a wavelet transformation as a basis for the separation. The signal, now free from respiration artifact, can then be reconstructed into the time domain. This method will be referred to as the Wavelet Source Separation method.

1.3 Background

All human systems exhibit a certain amount of variability. Among other systems, it is evidenced in the cardiovascular system, in the activation/deactivation of neurotransmitters and receivers resulting in behavioral changes and even in the circadian (day/night) cycle of sleep and wake. Typically manifesting itself as a change in power in a specific frequency range, the level of variability has been observed to be associated with various states of health and disease, ranging from behavioral to neurological to physiological abnormalities. In recent years, there has been an increased effort at

understanding this variability in terms of the amount of information that it can provide [1, 2, 3].

1.3.1 Physiological Research Studies

The term information is used in many ways in engineering. With respect to this research, it is in reference to the level of variability of the system. The level of auto-correlation of the data points in a time series is indicative of the amount of information contained within the signal. At one end of the spectrum, when data are too correlated, they become periodic. This indicates a low level of information within the system, because there is little to no variation from one point to the next and therefore gaining one small sample of data is sufficient to understand the entire system. At the opposite end of the spectrum is data that are not correlated at all, a state that is commonly referred to as noise. Somewhere between these two extremes lies the "healthy level of variability." In this state, there are sufficient interactions occurring within the system being investigated which preclude it from being described by one linear, time-invariant equation, but not enough interactions to preclude the system from being defined by one or a set of equations. While there is still disagreement about the level of correlation at which the signal becomes noise, there is agreement that in any system, a lower level of correlation is indicative of a higher level of variability, and thus, a higher level of information that is available to the researcher regarding the system status. The level of information contained within a signal is directly proportional to the level of complexity within the signal.

Research on physiological systems has begun to acknowledge that although it is

easier to model a system using linear parameters and models, it is not accurate and it is often not appropriate to assume that a physiological system behaves in a linear, stationary manner [4, 5, 6]. The reason for this is that biological systems vary with time. This is an adaptive mechanism which serves to protect the system from damage when environmental conditions change and place stress upon the system. An inability of the system to respond to stress, either real or perceived, is detrimental to the long-term survival of the organism. This inability to adapt is evidenced by depressed or exaggerated variability and complexity in a system [5, 7, 8, 9, 10, 11]. When the variability is too low, the system cannot respond effectively to the perturbation and will fail to provide an adequate level of physiological response over an extended period of time. When the variability is too high, the system overreacts to stresses and cannot recover properly. The problem that exists is that currently, there is little understanding of what is too low and what is too high, only that those states exist. Perhaps if more was known regarding the underlying neural processes that create this variability, it would become more apparent how to use this information as a tool to classify levels of health of a system.

The objective of this work was to investigate autonomic behavior at the system level as evidenced in the coupling of the cardiovascular and pulmonary systems in control and diseased populations, as well as the cardiac autonomic response to ANS stimulation via respiratory changes in an aging population that displayed varying levels of ability to adapt to the use of corrective lenses. Both populations displayed alterations in variability and control scheme at rest as well as with altered input from the respiratory system.

The manner in which this objective was accomplished was twofold. First, a toolset was developed with the express intent of deciphering underlying neural control processes for biological signals. This includes wavelet based entropy analysis combined with a data clustering technique for distinguishing between subject populations which can be employed in a clinical setting. The toolset also includes a wavelet based source separation (WavS) technique that extracts neural response information from stimuli signals, providing control system information that can be compared across subject populations.

The second step is to employ this toolset on clinically relevant data to delineate physiological changes in neural processes that occur during aging and disease. Specifically, it is of interest to understand how cardio-pulmonary interactions are altered with Chronic Obstructive Pulmonry Disease (COPD), a class of lung disease that incorporates emphysema, chronic bronchitis, or a combination of both. Further, it is of interest to determine how the cardiac neural control scheme is altered in the aging visual tracking system before and after the onset of the condition typically referred to as presbyopia, a stiffening of the lens of the eye or a weakening of the muscles that control the curvature of the lens or a combination of both. Presbyopia affects all people as they age, with the onset typically starting at the age of forty.

Traditional signal processing techniques are not appropriate in the analysis of biological signals because they are based upon the assumption that the signal being analyzed is stationary and/or linear, for ease of analysis. In reality the systems generating the signals, in addition to the signals that are generated, are often non-linear, time-varying signals. To account for this, efforts at investigating physiological systems can make the

assumption that the system is a black box [12], an assumption which can often lead to confounding and contradictory results. This research helps to open this box and investigate the activity of the systems within by using time-varying, non-linear analysis methods.

The tools that were developed in this research involve the use of wavelets, either through the analysis of the resultant time series generated as a result of performing a wavelet analysis, or via the use of a wavelet series as the basis of separation in a source separation and subsequent reconstruction technique. The methods were developed based upon a combination of non-linear techniques published in the literature and knowledge of the parameters of the systems to which they will be applied. Calculated wavelet coefficients were be used to determine the amount of information within the system via a Wavelet Entropy study. A cluster analysis of the data was then employed because it was hypothesized that it is possible to separate subjects according to various levels of health and age, based upon the information content, or variability, displayed by the system. This method proved able to classify subjects with greater than 90% accuracy.

The tools developed were used to analyze the neural underpinnings of two physiological systems that are both innervated by the autonomic nervous system. It is well known that cardio-pulmonary interactions are heavily interdependent. The typical measure of interdependence, also believed to be indicative of the level of activity of the parasympathetic nervous system, is respiratory sinus arrhythmia (RSA), which looks at the connection between variations in the heart rate and the respiration cycle. Currently, the gold standard method used in research of this phenomenon is limited to a Fourier analysis of power in the frequency range of 0.14 – 0.4 Hz [5, 13].

The neural control mechanisms that determine how the two systems are coupled and the control signal of the cardiac system remain unclear, as the gold standard seeks only to quantify, not specify, the level of activity resulting from stimulation. This research employs respiratory and cardiac data from populations that are healthy and also populations suffering from various degrees of Chronic Obstructive Pulmonary Disease (COPD). Using these data, the methods proposed in this research will attempt to remove the respiratory signal from heart beat fluctuations using a blind source separation technique. This should enable fuller analysis of the neural control signal that is present, since it is believed that the fluctuations in the heart rate signal are a result of the interaction of the branches of the autonomic nervous system and the respiratory system. It is proposed that this technique will enable investigation of changes that occur in disease and aging, particularly with regard to the neural input to the heart when the lungs are damaged and with respect to populations with decreased adaptability evidenced in other systems influenced by the autonomic nervous system. As will be seen, the signals change in amplitude, phase and frequency with various stimulations and levels of health.

The results of the information analysis were effectively implemented to objectively categorize varying levels of health within the disease population. It also validates variability theory by setting different levels of variability for health and disease. In an effort to investigate the influence of the autonomic nervous system (ANS) on the body, activity in the cardio-pulmonary system, known to be influenced by the activity of the two branches of the ANS, will be investigated simultaneously. It was hypothesized that the two systems will display similar changes in disease. The method employed to investigate whether there are cardiac differences in apparently healthy subjects who are

able to adapt to visual tasks is a standard controlled breathing task. This experiment is significant because there have not been experiments that specifically examine system level interactions of the ANS. Studies of the ANS input to the visual system are not reported in the literature, although ANS input to the cardiovascular system has been reported extensively. This study builds upon a vast pool of knowledge of autonomic activity in one physiological area to understand farther reaching implications of the system to indicate that the physiological variability that has been observed and attributed to the interacting branches of the ANS may influence the levels of adaptability in systems other than the cardio-pulmonary system. The findings of this study suggest that cardiac autonomic response differences may be measurable, even in apparently healthy individuals, when investigating adaptability in other systems influenced by the autonomic nervous system.

Controlled breathing was performed by having the subjects follow a light emitting diode (LED) display placed in a dark room, such that the LEDs were placed parallel to their line of sight. The subjects were instructed to control their breathing to match inspiration to the lights on the LED display when they illuminate in the direction toward the subjects, and expiration to match the outward travel of the LED display. The electrocardiogram (ECG) and respiration signals were be recorded to investigate the cardio-pulmonary interactions. In order to appreciate why this work is important, it is necessary to understand what is known about the physiological systems discussed above, as well as the changes that are known to occur in the systems with disease and aging. There is a vast amount of knowledge of the system and diseases that affect it that exists, and yet neural influence remains largely a mystery. Chapter two discusses the systems,

changes that occur in them with aging and disease, and the methods that are proposed to investigate the ANS activity.

1.3.2 Signal Processing Research Studies

The wavelet entropy analysis applied in this research was applied by Kowalski, et al., in an effort to determine the classical and quantum interface of particles. As the system consists of coupled oscillations, the wavelet entropy method was employed to determine if the change from classical to quantum particle behavior could be detected using the information level contained within specific bandwidths [54]. This application was significant because it attempted to quantify non-linear coupled interactions using wavelet entropy, and was the basis for the application of the method in this research.

The wavelet entropy approach has also been employed in physiological applications such as scalp electroencephalogram (EEG) analysis for detection and analysis of seizures, event-related potential derived from the EEG (ERP), using the electrocardiogram (ECG) to differentiate normal from ischemic episodes, and cardiac valve disease analysis [96, 98, 99, 100]. It has not been used to classify patient populations in an effort to augment clinical toolsets, as is done in this research.

Some of the earliest applications of wavelets were for denoising and compression of data, and those applications continue to be prevalent in the literature [111, 110]. This research employed the theory of wavelet denoising with a priori knowledge of the noise signal, which in this case is the respiration influence in the interbeat interval. The influence of respiration on the HRV signal has been a confound in research and has been investigated [104, 105, 108, 109]. Barbieri's group investigated the use of time-varying spectral analysis to quantify continuous respiration and baroreflex influences of heart

rate. This group was able to model the influence of respiration, but not to quantify the underlying dynamics of the physiology. Byrne, et al. quantified RSA using a peak-valley estimator, which did not have good time resolution. This resulted in errors in the analysis when short time-periods were being investigated, or if analysis of transient episodes was required. Of note is the finding by Min that the LF and LF/HF ratios were elevated in subjects with hypoxia. The finding is in agreement with the findings regarding the COPD population in this research, which found that after removal of respiration the LF content was higher in COPD than control subjects, driving the LF/HF ratio higher after the analysis. Further, in healthy subjects, LF/HF ratio was lower after removal of respiration due to the removal of low frequency content as well as high frequency content. Nagata, et al. used neural networks to observe that sympathetic activity dominates during vigorous conditions, while 19 markers of general autonomic activity declined during fatigue. The question remains, however, whether the increase in sympathetic activity was respiration mediated.

Methods to derive and quantify the respiration signal based upon ECG and/or blood pressure waveforms have been presented, but methods to remove the influence of respiration from the IIBI signal are limited [103, 106, 107, 112]. DeMeersman et al. derived a method of estimating respiratory information from the pulse signal. This method quantified, rather than using as a basis for extraction, the respiration signal. As a first phase of analysis, when only the pulse information is available but not the respiration data, this method may be used in conjunction with the separation method developed in this research. Yildiz et al. developed a model that assessed respiratory influence on HRV. Significantly, as with Min's finding, the model analysis derived

significant influence of respiration over the HF peak, but also plays an important role in the genesis of the LF activity. The group also suggests that LF/HF ratio may not be a suiTable measurement of sympatho-vagal tone unless there is first a respiration correction performed in the HRV data.

Time-frequency methods have successfully been employed to perform blind-source separation of signals [115, 116]. Belouchrani and Amin developed an algorithm to remove noise from signals. The basis for their work was to employ the distribution of noise in the time-frequency domain, and the local frequency activity the source signal to remove the noise from the signal. In the case of HRV analyses, the "noise" is a continuous signal throughout the course of the entire signal, with spectral power in the same region as the signal of interest. Zhang and Amin use time-frequency distributions to whiten the signals and for subsequent separation of the source signals. The limitation is that the time-frequency distributions of each of the signals must have disjoint distributions. In the WavS method, the similarity of the time-frequency distributions is exploited to separate the two sources.

1.4 Significant Contributions of this Research

With regard to central autonomic pathways, evidence was presented that the removal of respiration does not remove the entire variability from the signal. Further, cardio-pulmonary correlation in controls is measurably different from that of COPD subjects, evidenced by different minimum requirements for correlation required to effectively separate the respiration from the heart rate variability signal. The level of complexity in the HRV signal is also distributed differently in COPD than in the control population.

The distribution of the complexity in specific frequencies is significant during exercise, while the actual entropy values are the significant components employed to distinguish between COPD and control populations at rest.

With regard to the peripheral and central autonomic link, several key findings of this research goal exist. First, the presbyopic group unable to adapt to the use of lenses exhibited different HF content than the adaptive presbyopic and control groups. In addition, the non-adaptive presbyopic group exhibited lowered levels of heart rate variability, as evidenced by standard deviation and HRV markers of HF, LF and LF/HF ratio, in comparison to the control and adaptive presbyopic groups.

Finally, wavelet statistical methods possess significant potential in applications to cardiac autonomic function. The wavelet entropy method was able to classify patient populations with classification rates of 93% and 100% for resting and exercising populations, respectively. With regard to wavelet source separation, the potential of this method to delineate autonomic modification with disease is very significant. The model indicated a 0.9988 correlation between the original subcomponent of interest and the signal that the WavS program extracted. The presbyopic data, which were controlled to three different breathing rates, resulted in decreased low frequency HRV marker when breathing at 8 breaths/min, and decreased high frequency HRV markers when breathing at 12 and 16 breaths. This validates the method clinically due to the removal of spectral content relative to the breathing influence that was created. The COPD study yielded interesting results, which point to other mechanisms underlying the variability in the

timing of successive heart beats. This information was confounded previously by respiration. The WavS holds significant potential for future research, in cases where the influence of respiration is unclear.