

## CHAPTER 5

### CONCLUSIONS

There were three main hypotheses of this research. First, the research sought to examine changes in central autonomic influence during pulmonary disease. Next, links between central and peripheral autonomic control were investigated. Finally, the research sought to provide tools to enable the clinical quantification of level of disease and classification of subject through these objectives, and to provide new insight into those mechanisms with novel wavelet statistical measures.

#### 5.1 Central Autonomic Influences

The first goal of the research was to provide new insights into the *central* autonomic influence over cardio-pulmonary interactions (COPD population). It was hypothesized that different information content, or entropy, existed in specific frequency ranges depending on the subject's level of health. Also, this distribution of entropy varies with subject population and can be classified statistically, enabling computer-aided separation of clinical populations. It was hypothesized that HRV markers would be altered during aging and disease. It was further hypothesized that the Wavelet Source Separation method would alleviate the need to perform controlled measures like paced breathing during clinical assessments of health. This would in turn allow researchers to investigate the dynamics of the system during activity without concern for respiratory effect.

The results indicate that wavelet entropy can be used effectively to characterize central autonomic influences and objectively separate clinical populations with a high level of

accuracy. This is supported by the impressive performance of 93% classification accuracy of COPD study participants at rest and 100% classification accuracy of COPD study participants during exercise using the both the wavelet entropy values and the distribution of that entropy across frequency sub-bands as the input to the cluster analysis.

Changes in COPD and control autonomic markers are, in fact, evident after respiration is removed. LF/HF ratio slightly decreased on average from pre to post reconstruction for controls, increased (sometimes significantly) on average for COPD. In healthy controls, respiration frequency seems to vary, causing large decreases in LF and HF autonomic markers. This results in the LF/HF ratio decreasing significantly after the removal of the respiration artifact from the data. With respiration effect removed from COPD population data, LF dominates autonomic response. Subsequently, this results in a significant increase in LF/HF ratio in COPD due to the concurrent decrease in HF content as a result of respiration removal.

A decrease in variance by orders of magnitude after the removal of the respiration increases the probability that smaller changes can be detected in values. This can have a significant impact on data sets where the intra-subject variability is quite high, confounding the data sets and reducing the likelihood of significant findings in a study. It may also indicate that the physiological response to respiration, in terms of mechanical and chemical alterations, may be a large contributing factor of differences in levels of health rather than direct sympatho-vagal influence.

It is hypothesized that the signal content that remains after the removal of direct pulmonary influence may be indirect indicators of the indirect influence of respiration

through mechanical and chemical pathways on HRV. The link between chemoreceptors and mechanoreceptors in modulation of heart rate cannot be overlooked. Sections 2.1.4 and 2.1.5 provide the physiological basis of this statement. The outcome of this study suggests that the direct influence of respiration is not the only component driving the high frequency or, interestingly, low frequency content of the HRV signal which serve as the markers of cardiac autonomic response. The collective outcome of this segment of the research suggests that the direct influence of respiration may mask other indirect indicators of respiratory influence occurring through chemical and mechanical pathways and new insights into autonomic function in disease may be obtained with these methods.

## 5.2 Central and Peripheral Autonomic Linkage

The second goal of the research was to provide new insights into the links between *central* and *peripheral* autonomic influence. It was hypothesized that peripheral autonomic influence over the visual system is linked to the central autonomic influence over cardio-pulmonary interactions, and that this link would be evidenced by a decrease in HRV in people with lower levels of oculomotor adaptability.

As a result of the assessment of pilot data obtained from the presbyopic population, there is strong evidence in favor of a correlation between peripheral and central autonomic influences on HRV, as evidenced by oculomotor adaptability. There are several results that support the linkage hypothesis.

The first result is the standard deviation of the data sets across populations. Differences between populations were quantified, not between age group as is the typical assumption, but rather by level of oculomotor adaptability. The standard deviation of the

adaptive presbyope and control data sets displayed similar trends at increasing frequencies of controlled breathing. The non-adaptive presbyopes showed significantly lower values at the higher respiratory frequency of 16 [bpm]. This suggests that controls and adaptive presbyopes have similar sympathetic responses. The question that remains to be answered is in what way the sympathetic response of non-adaptive presbyopes varies from that of the adaptive presbyopes and controls.

Not unlike the COPD data set, the presbyopic population displayed different autonomic markers before and after the respiration was removed from the IIBI signal. As with the COPD population, the frequency content did not completely disappear in the reconstructed IIBI data sets with the effect of respiration removed. This suggests that a mechanism other than pure sinus arrhythmia is driving the variability at all breathing rates. Of significance is that the autonomic markers for each breathing rate were different from each other after the removal of respiration. If they were the same, this would indicate that the primary influence of the variability is the respiration. The fact that they are different supports, once again, the hypothesis that there may be something more than respiration driving HRV. A larger data set must be employed to validate whether the differences in autonomic markers after respiration extraction are significantly different between various controlled breathing rates.

The subjects in the presbyope group displayed some interesting, and in some cases significant, trends in the WavS methods, although the sample size must be larger to accurately assess the results obtained. In addition, it would be of interest to assess entropy levels after the influence of the respiration is removed. This would address questions regarding the influence of respiration in the level of variability in cardiac

oscillations. Based upon the findings of this research, it is hypothesized that the levels of entropy would be greatly reduced after removal of the respiration. However, the variance in the series would also be reduced and would likely yield significant results regarding even small changes in the vagal modulation of HRV.

### 5.3 Wavelet Statistical Methods

The final goal of this research was to assess the utility of novel Wavelet Statistical Methods with respect to cardio-pulmonary dynamics. This included the development and application of wavelet statistical measures to aid in assessment of autonomic health. This was accomplished in two ways:

- a. Development and application of wavelet entropy measure specifically with application to HRV, and combination of this with k-means cluster analysis for separation of level of health of clinical populations. Entropy and density distribution of energy within and between specific bandwidths can be used to separate clinical groups.
- b. Specific frequency of respiration and HRV signal components correlate highly in time. This correlation can be used to remove the confounding influence of respiration from central autonomic neural control signals.

This research indicates that there is significant potential for wavelet based statistical measures applied to cardio-pulmonary dynamics to provide information that can be implemented clinically for computer-aided assessments of autonomic health.

The wavelet entropy method possesses potential for classification of level of health because it employs not only the complexity measure of entropy, but also incorporates the distribution of complexity in different bandwidths into the classification. This resulted in a highly accurate classification scheme.

The model illustrates the power of the WavS analysis. As a result of the model analysis, many considerations important in the development of the WavS algorithm, as discussed in Chapter 3, were evaluated for significance in the algorithm. The model served as a validation that the analysis could be performed, with a high level of accuracy, on dynamic signals to separate a known component from a signal.

The first validation of the WavS method came from the model, where the correlation between the input and the reconstructed signals was 0.9988. The method was able to capture changes in frequency content due to changing respiration with a high level of accuracy. The second validation of the WavS method came from the presbyope population in the differences between autonomic markers at different breathing rates. WavS reduced frequency content in ranges concurrent with breathing rate, indicating a robust analysis. The WavS method reduced frequency content in ranges concurrent with breathing rate, indicating a robust analysis. Specifically, at 8 [bpm], which is a content in the LF range, the LF autonomic marker is the only one that showed significant changes after the removal to the respiration signal. Further, at 12 and 16 [bpm], which are evidenced in the HRV spectrum as content in the HF range, the HF autonomic marker is the only one that showed significant, or nearly significant, changes after the removal to the respiration signal. This suggests that the WavS method successfully removes the influence of respiration from clinically obtained data.

The main intent of this aspect of the research was to determine if the respiration effect could be removed from the IIBI signal. The model results indicate that this can be done. However, what clinical implications for diagnosis does this method possess? The two subject populations yielded some striking results, but again, the research was a pilot

study by design, and the sample sizes were not robust enough to form any statistical determinations. However, interesting trends exist and should be further investigated via the use of a larger sample size.

A significant outcome of the model, as well as in both subject populations, is that even with a spread spectrum respiration signal, the analysis was able to separate the respiratory from the cardiac fluctuations. The respiration spectra were illustrated in Chapter 4, including the standard Fourier content measures as numerical validation, and it is clear that the overlap was removed for small and large band peaks in the spectra. Of particular interest is the fact that some frequency activity is still evident at specific frequencies that must be attributed to the cardiac cycle, as the bulk of the respiration spectral activity is removed from the IIBI spectra. Further investigation should be performed in the assessment of changes in the ratio, as the values for each group are now much closer together. The algorithm performed in a normalizing capacity by removing large fluctuations induced by the pulmonary system and revealing underlying cardiac autonomic function. With a smaller variance, smaller changes in mean value can be detected and therefore, a smaller sample size can be used for analysis.

The COPD population was characterized by a significant difference in values of HF and LF between the two groups. The minimum correlation threshold necessary to separate the signals varied according to subject population. As a result, the lower end of the correlation range was used for both sets of data. The correlation for the COPD subjects often went as low as 0.6 and the healthy subjects were able to employ an average separation threshold of least 0.8. Specifically, the larger removal of LF content in the control population than in the COPD population leads to questions of whether

sympathetic stimulation occurs in COPD patients with each breath, as opposed to the LF content being an artifact of the noise. Interestingly, Min et al. found that acute hypoxia in fetal lambs increased low-frequency and LF/HF ratio content, suggesting an increased sympathetic activation compared with baseline [105]. The results of this research indicate that the LF content may represent true sympathetic content in the COPD population, where it may be more driven by sinus arrhythmia in controls.

The WavS method showed some interesting trends in terms of the Presbyope population data. Of significance is the change in each of the cardiac response parameters. Although the samples size was not large enough for statistical significance, there are some notable results. It is of significance that the separation algorithm employed a correlation value of 0.85 for each subject as it was assumed that they were all ostensibly of the same general level of health. There were different levels of signal separation for each group based upon the level of correlation, which is evident in the varying degree of change in frequency content values from one breathing rate to another. It may also be appropriate to investigate non-linear correlation measures to more fully capture trends over larger windows of time.

In addition, the onset adjustment varied from population to population, suggesting the existence of some intrinsic factor that differs among populations, which resulted in a delay the cardiac loop. The same differences in both onset time and level of correlation were seen for both presbyopic and COPD populations. Although a certain degree of that is due to the change in signals from ECG to IIBI, there is a certain degree that is unaccounted for. Alterations in the cardio-pulmonary tissue may account for the change

in onset time as the system ages or is diseased and should be investigated as a possible source for the variation.

There are points within the signals of both populations during which the respiration and ECG lose coordination, even during steady state. Although the signals typically return to the coordinated state, there are significant points during which control and subject populations have a decrease in the level of correlation of their cardio-pulmonary dynamics. Perhaps the threshold must be adaptive to account for this. Perhaps this loss of coordination, and the extent to which this loss occurs, may yield significant information regarding autonomic control.

It is also evidenced that if the signals are out of phase with each other, the signals are not separated in the WavS algorithm, although the program performs well for respiration signals that are 180 degrees out of phase. This occurs even if there is a significant peak in the HRV spectrum that correlates with the respiration peak in the Fourier domain. When the signals are aligned, the separation accuracy increases. It is possible that a wavelet spectral alignment occurring before the analysis would improve the robustness of this analysis.