INVESTIGATION OF RATE PRESSURE PRODUCT AS A METRIC TO QUANTIFY CARDIAC WORKLOAD IN SLEEP APNEA EVENTS

By

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ABSTRACT

INVESTIGATION OF RATE PRESSURE PRODUCT AS A METRIC TO QUANTIFY CARDIAC WORKLOAD IN CLOSE PROXIMITY SLEEP APNEA EVENTS

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An investigation on the use of rate pressure product (RPP) to measure the cardiac workload in sleep apnea patients is presented. RPP is the product of systolic blood pressure (SBP) and heart rate (HR). The application of RPP to quantify cardiac workload is combined with the detection of respiratory events occurring in close proximity (less than 30 seconds apart). Close proximity events are referred to as respiratory event chains (RECs). Statistical analyses were conducted on various RPP metrics as well as SBP and HR to determine if there were significant differences between cardiovascular function during RECs and isolated events (greater than 30 seconds apart).

The results show possible evidence of increased variability in RPP and SBP during REC events as compared to isolated events. However, these trends varied across subjects and the findings were inconclusive. Average RPP, HR, and SBP were not found to vary significantly between REC and isolated events. Correlation between the ratio of respiratory events to recovery, referred to as temporal event fraction ratio (TEFR), and RPP showed possible relationships between RPP variation and TEFR. But once again, the results are inconclusive and require further investigation.

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CHAPTER 1

INTRODUCTION

1.1 Sleep Apnea

1.1.1 What is Sleep Apnea?

Sleep apnea is a disorder which causes arousals from sleep due to a lack of airflow. Cessation of breathing causes changes in blood gas levels, leading to hypoxemia and hypercapnia. which triggers an arousal from sleep [1]. For a patient to be diagnosed with sleep apnea, they must have repetitive episodes of restricted or paused breathing lasting more than 10 seconds. Repetitive episodes of sleep apnea disrupt the sleep cycle and have many negative consequences on health such as hypertension [2]. Factors that contribute to the risk of sleep apnea include obesity, male sex, age, and menopause.

1.1.2 Types of Sleep Apnea

There are three main types of sleep apnea: obstructive sleep apnea (OSA), central sleep apnea (CSA), and mixed sleep apnea. OSA is the most prevalent sleep apnea type among all demographics [3]. OSA is caused by a collapse of the upper airway due to muscle relaxation during sleep, particularly those in the tongue and soft palate. In OSA respiratory drive is still present; however, there is simply an obstruction preventing air from flowing through the pharyngeal lumen. The risk of developing OSA significantly depends on upper airway anatomy. A narrow pharyngeal lumen is associated with increased risk for OSA, especially if accompanied by excessive fat deposits from obesity [4]. The factors involved in CSA lie in the nervous system, where the drive to breathe (respiratory drive) is reduced or blocked completely [5]. As a result, a patient will stop breathing not because of an obstruction in the airway, but because of central nervous system malfunctions. Mixed apnea occurs when there are interactive effects between concurrent OSA and CSA events. Mixed sleep apnea is not categorized as a separate disease, rather, it is grouped with obstructive sleep apnea/hypopnea syndrome (OSAHS).

1.1.3 Consequences of Sleep Apnea

The disruption of sleep caused by sleep apnea affects the body in many ways. Constant episodes of obstructed breathing can keep blood pressure elevated throughout the night [6]. This stress puts patients at risk for hypertension and cardiovascular disease [2]. Apart from the effects on the cardiovascular system, disturbed sleep prevents patients from entering all the necessary stages of sleep required to maintain cognitive performance. Day-time sleepiness, lack of concentration, depression, and various other sleep deprivation-related conditions can be caused by sleep apnea [7].

1.1.4 Detection and Treatment of Sleep Apnea

Diagnosis of sleep apnea is conducted by studying data from a patient's various cardiorespiratory and neurological signals over an entire night of sleep using various biosensors and digital devices. This measurement procedure is known as polysomnography (PSG). The data from the PSG is studied by a certified sleep professional, and respiratory events are identified based on the data. Guidelines for scoring apnea events are provided by the American Academy of Sleep Medicine [8]. Sleep apnea severity is assessed by the apnea hypopnea index (AHI). The AHI is the average of the count of apnea/hypopnea events occurring in a patient per hour of sleep. A table with apnea severity and corresponding AHI ranges is presented in Table 1.

Table 1 Apnea severity and corresponding AHI ranges. From [9].

Apnea Severity	
None/Minimal	AHI < 5 events/hour
Mild Sleep Apnea	5 events/hour ≤ AHI < 15 events/hour
Moderate Sleep Apnea	15 events/hour ≤ AHI < 30 events/hour
Severe Sleep Apnea	30 events/hour ≤ AHI

The AHI is a standard metric for diagnosing sleep apnea and its severity. However, some researchers have expressed concern over the AHI and its oversights on important clinical features [10].

Currently, continuous positive airway pressure (CPAP) machines are the primary treatment option for sleep apnea. The machine delivers air through the nasal passages via a mask; the column of air exerts pressure on the pharyngeal airway and keeps it open. While CPAP therapy is effective, there is a problem with patient adherence to the therapy, often due to discomfort from wearing the device [11].

1.2 Cardiovascular Metrics

1.2.1 Arterial Blood Pressure

Arterial blood pressure is the pressure exerted by blood on the arterial walls and depends on heart rate, cardiac stroke volume, and peripheral vascular resistance [12]. The two main BP components considered for cardiovascular health are systolic and diastolic BP. Systolic blood pressure (SBP) occurs during the peak of heart contraction and is the highest blood pressure observed during a cardiac cycle. Diastolic blood pressure (DSB) is the lowest blood pressure observed and occurs when the heart is relaxed. Blood pressure values are typically presented with units of millimeters of mercury (mmHg) in a systolic/diastolic format. The normal range for blood pressure is around 120 mmHg for SBP and 80 mmHg for DSB (120/80 mmHg).

Blood pressure varies considerably throughout the day, but a chronic pathologically high blood pressure is known as hypertension and can cause a variety of complications including heart attack and stroke [13]. The categories of hypertension are provided in Figure 1. Sleep apnea is known to cause hypertension, and some sleep apnea patients develop resistance to antihypertensive medications [2].

Blood Pressure Category	Systolic Blood Pressure		Diastolic Blood Pressure
Normal	<120 mmHg	and	<80 mmHg
Elevated	120-129 mmHg	and	<80 mmHg
Hypertension			
Stage 1	130-139 mmHg	or	80-89 mmHg
Stage 2	≥140 mmHg	or	≥90 mmHg

Figure 1 The stages of hypertension. From [14]

In addition to hypertension, sleep apnea events have been found to cause transient rises in blood pressure 5-10 seconds after the event ends [15].

1.2.2 Heart Rate

For most clinical applications, heart rate (HR) is defined as the number of heart beats occurring in one minute. We computed the instantaneous heart rate using the inverse of the R-R interval. As with blood pressure, HR contributes to cardiovascular health and chronically high HR can increase cardiac workload and stress on the heart [16].

1.2.3 Rate Pressure Product

Rate Pressure Product (RPP) is a metric used to measure myocardial work and is obtained by multiplying systolic blood pressure and instantaneous heart rate [17]. The equation for RPP is found in section 2.3.3. RPP is correlated with myocardial oxygen consumption, and an excessively high RPP has been linked to ischemia, infarction, and other cardiovascular complications [18]. The implications of RPP for sleep apnea are not as well documented as BP, but some researchers have found a rise in RPP immediately following the end of respiratory events [15]. In healthy subjects, RPP has been found to follow a circadian rhythm similar to that of blood pressure and heart rate, dipping to its lowest value a few hours before waking and peaking in the afternoon [19].

The negative impacts of sleep apnea on cardiovascular health are reflected in the RPP. Smith's group [20] found that rises in myocardial work (RPP) following respiratory events had significant impacts on the structure and function of the left ventricle. These impacts have long term implications for cardiac efficiency and could contribute to day-time hypertension and other negative cardiovascular effects. Hamilton's group identified a delay between RPP response and coronary blood flow during OSA events [15] which caused an increase in coronary vascular resistance. The group hypothesizes this disconnect between coronary blood flow and RPP could explain the prevalence of nocturnal ischemia in sleep apnea patients. As observed in these studies, RPP is a reliable method for quantifying the effects of sleep apnea on the cardiovascular system.

Outside of sleep apnea, RPP has been used in conjunction with SBP and HR to investigate many aspects of cardiovascular health. For example, the role of SBP and HR in heart failure with preserved ejection fraction is still misunderstood. One group used RPP to clarify these misunderstandings and find associations between heart failure outcomes and SBP/HR [21]. RPP has recently been applied to measure performance in stroke patients. By combining RPP with oxygen pulse measurements, researchers were able to explain 79% of the variance in energy expenditure during exercise for patients with chronic stroke [22]. These findings have significant applications for rehabilitation and metabolism research. RPP has also been utilized to study the effects of ischemia (lack of blood flow). Myocardial reperfusion injury occurs when the heart first undergoes ischemia; then as blood flow is rapidly restored, the myocardial tissue is damaged. In one porcine study which measured myocardial infarct size (tissue death) following artificially applied ischemia, cardiac work (RPP) was strongly correlated with the infarct size [23].

1.3 Study Overview and Organization

1.3.1 Study Objectives

The primary goal is to investigate rate pressure product (RPP) as a metric to study the effects of sleep apnea events on the cardiovascular system. Specifically, we conducted comparisons between respiratory events that were within close proximity of one another, and events that were isolated. Events identified as being in close proximity are referred to as respiratory event chains (RECs). We hypothesized that the rapid occurrence of apnea events during RECs would cause a magnified response in cardiorespiratory feedback. The effects of this magnified response would be reflected in the cardiovascular metrics mentioned previously including RPP. To detect any significant differences between RECs and isolated events, we designed metrics for RPP as well as SBP and HR.

1.3.2 Thesis Organization

Chapter 2 describes the methods for the study including polysomnography and collection of nocturnal blood pressure data. Experimental setup is described as well as subject demographics, algorithm logic for digital data processing and statistical methods. Chapter 3 details the results of statistical analysis and the computations described in Chapter 2. Chapter 4 provides a discussion of the results of the study, implications for sleep apnea research, consideration of future work, and conclusions.

CHAPTER 2

MATERIALS AND METHODS

This chapter describes the methods for measuring and analyzing the impact of sleep disordered breathing (SDB) on cardiovascular response in a sample of OSA patients. The chapter begins with the experimental setup including polysomnography data collection and patient demographics. Section 2 provides an overview of the device used to measure NBP as well as reasoning for using a non-invasive method. Section three provides definitions of respiratory events and criteria used in detection of the respiratory event chains (RECs). The final section describes methods for statistical analysis and comparing metrics between isolated events and RECs. Additionally, mathematical definitions for the various metrics used in statistical analysis are provided.

2.1 Subject Demographics

The study was conducted with 13 OSA subjects who underwent 8-hour polysomnography at Sleep Consultants, Inc. (Fort Worth, TX). IRB approval was obtained for the study and approved consent forms were signed by the subjects. The subject demographics are displayed in Table 2.

Table 2 Subject Demographics

Col. 1 Subject	Col. 2 Age (yr)	Col. 3 Weight (lb)	Col. 4 Height (cm)	Col. 5 BMI (kg/m^2)	Col. 6 Medications	Col. 7 Sex	Col. 8 AHI
1	66	240	177.8	34.4	None	Male	73.5
2	48	325	175.3	48	Coreg; Ramipil; Spirondactone; Vit D3	Female	42.3
3	62	210	190.5	26.2	Not Recorded	Male	44.9
4	50	174	180.3	24.3	None	Male	18.3
5	50	175	175.3	25.8	Crestor (10mg); Proglitazine(15mg); Janumet 50/1000	Male	63.6
6	39	225	188	28.9	None	Male	42.8
7	56	298	182.9	40.4	None	Male	105.4
8	54	195	154.9	36.8	None	Female	31.1
9	47	235	175.3	34.7	Took half a sleeping aid pill but patient did not know the name	Male	77.4
10	56	290	182.9	39.3	Metoprolo; Provastatin; Phelofibrate	Male	87.3
11	54	215	170.2	33.7	None	Female	45.5
12	45	210	162.6	36	None	Male	82.2
13	57	248	162.6	42.6	Prozac; Estradiol	Female	21.8
Mean ± SD	52.6 ± 7.2	233.8 ± 46.5	175.3 ± 10.4	34.7 ± 7.0	---	---	56.6 ± 27

2.2 Non-invasive Blood Pressure Instrumentation

The study required a reliable way of continuously measuring nocturnal blood pressure (NBP) surges in sleep apnea patients while they experienced SDB during sleep. Invasive methods such as arterial catheters provide greater precision and less variation than noninvasive measurements. These advantages are significant, especially in the context of precise hemodynamic response [24]. However, given the variable conditions during sleep, invasive methods carry the risk of infection and bleeding if the arterial line is dislodged. Therefore, non-invasive methods are preferred for sleep study.

2.2.1 Continuous Non-Invasive Blood Pressure Measurement

Continuous, non-invasive blood pressure measurements are based on two main methods: arterial applanation tonometry (AAT), and the volume clamp method [25]. The AAT method employs a transducer secured over an artery that traverses the bone, allowing the device to measure differences in force and pressure caused by blood flow. Not all AAT devices are able to measure blood pressure continuously. The T-line system [26] is one example of a continuous implementation of AAT. The volume clamp method uses a finger cuff containing a photodiode which is attached to either the index, middle, or ring finger. The photodiode measures the diameter of the artery, and the cuff applies a pressure to keep the diameter of the artery constant. With this method, a blood pressure waveform is created and cross-referenced with a brachial artery measurement measured by a separate finger cuff [27].

2.2.2 Finapres overview

Overnight blood pressure measurements were conducted using the Finapres, a non-invasive blood pressure measurement device that has been validated against both invasive and non-invasive methods [28]. The Finapres measures continuous beat-to-beat blood pressure. Furthermore, the Finapres incorporates signal processing methods such as filtering and level correction which considerably improve performance in unstable conditions. The Finapres implements the volume-clamp method to dynamically measure differences in volume around the arteries in the finger [28]. This device has been used in many clinical studies and various physiological research studies such as modeling of cerebral autoregulation [29].

The Finapres uses two finger cuffs. The main finger cuff is placed on either the index, middle, or ring finger to obtain the most accurate measurements (Figure 2). This cuff is secured with a Velcro strip and is centered on the middle phalanx. The patient should experience a slight pulsatile sensation when the device is operating, but not excessive discomfort. The second finger cuff (Figure 2) belongs to the heart reference system and functions as a supplementary sensor the Finapres uses for height compensation when a patient moves their arm. Calibration, filtering, and the efficiency of data processing techniques in the Finapres depend on proper finger cuff positioning.

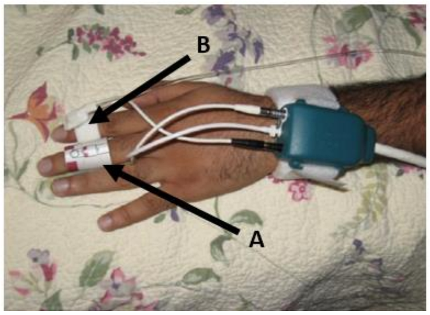

Figure 2 Application of Finapres cuffs. “A” points to the main cuff containing the photoplethysmography unit, and "B" to the cuff used in the heart reference system.

For greater accuracy, the Finapres performs periodic automatic calibrations, usually lasting between 2-3 seconds. Calibration periods contain no useful data and should be identified as such in the data analysis. Chuang’s algorithm [30] overcomes this obstacle by calculating the temporal distance between all blood pressure peaks and storing them in a histogram-type distribution. Due to their relatively large duration, calibration periods will show up on the extreme end of the temporal distance distribution. In this manner, the calibrations are easily identified and omitted from data analysis. For more detail, see Chuang [30].

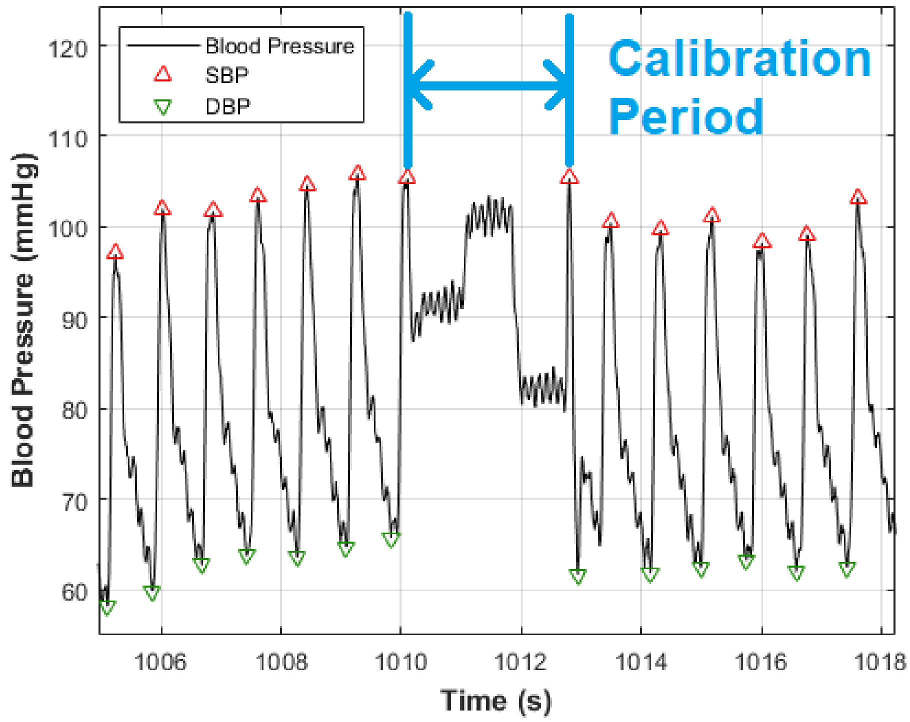

Figure 3 Example of a calibration period. These periods lack any meaningful data and are excluded by Chuang's algorithm to avoid problems in data analysis. Adapted from [30].

2.3 Experimental Setup

This section will describe the setup for the sleep lab polysomnography as well as data processing and synchronization.

2.3.1 Polysomnography

Data for the study were obtained from an accredited sleep lab (Sleep Consultants Inc., Fort Worth, TX) where sleep apnea patients underwent 6-8 hour polysomnography (PSG). The PSG channels were measured using the proprietary Sandman Elite PSG software (Natus, Pleasanton, CA) and consist of the following: electroencephalogram (EEG) with C4/A1 and C3/A2 electrodes, electrocardiogram (ECG), electromyogram (EMG), electrooculogram (EOG), abdominal and chest movement, oral and nasal airflow and snoring [31]. Continuous blood pressure measurements were made concurrent with PSG data using the Finapres (DEMCON, Netherlands).

The Finapres is a noninvasive blood pressure measurement device that uses finger cuffs to collect beat-to-beat blood pressure. The analog to digital converter DAQ 6024E unit was used to collect the blood pressure data as well as oxygen saturation (SpO_2) and CO_2 at a sampling rate of 1kHz. The unit contains two 24-bit counters, 8 digital input/output lines, and two 12-bit analog output lines [30].

2.3.2 Data Processing

PSG data from the Sandman software and DAQ card were digitally stored using a custom LABVIEW program. Once the features were captured in LABVIEW, the files were stored in binary format and transferred to MATLAB. Since the channels had different sampling rates, both the Sandman PSG and DAQ card BP data were resampled to 128Hz in order to maintain consistent, synchronized signals for all the channels. To ensure synchronization between the blood pressure and polysomnography data, a reference synchronization signal was generated and linked to both datasets [31]. Data from the polysomnography channels were used by the sleep lab to mark the temporal locations of respiratory events. This event marker scoring was stored along with the rest of the polysomnography channels and is critical to the detection of the RECs. A sample of event marker scoring with all event types is illustrated in Figure 4.

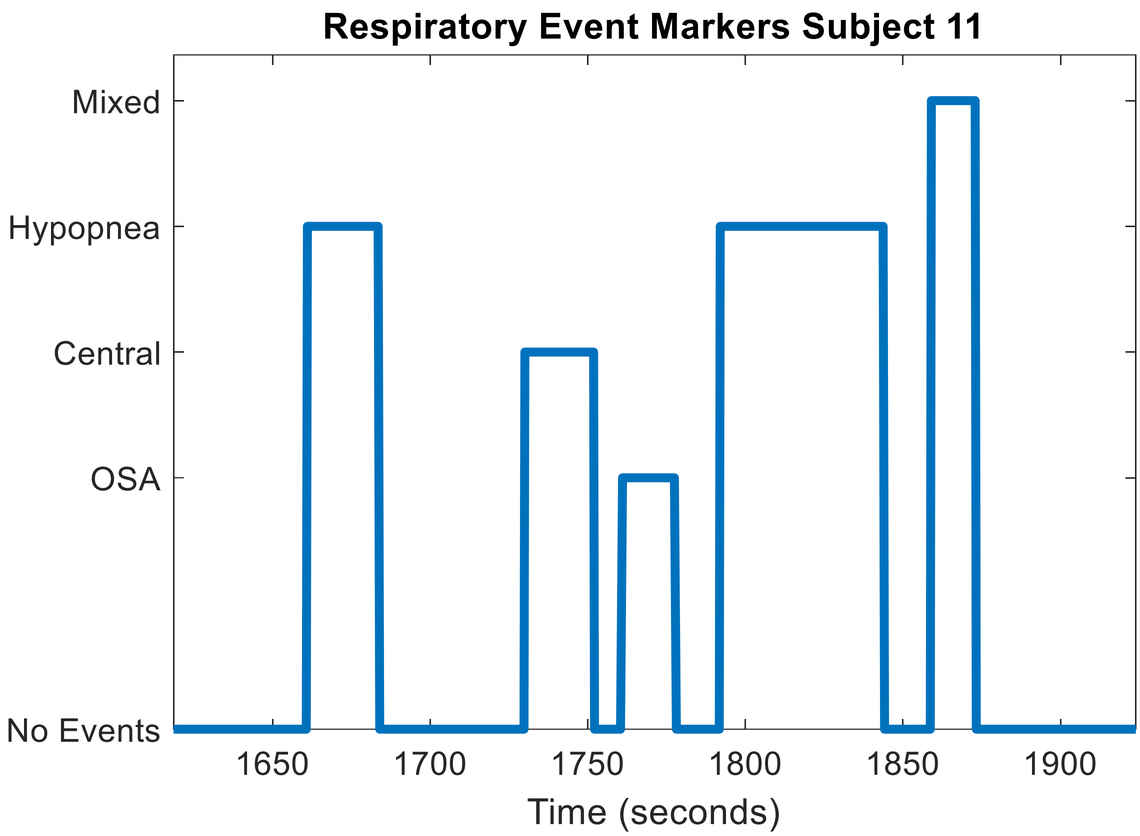

Figure 4 Respiratory event markers in subject 11. Each vertical bar represents the occurrence and duration of a specific type of apnea event. The periods of flat lines are recovery periods. In this example, there are two hypopneas, one OSA, one central apnea, and one mixed apnea.

2.3.3 Blood Pressure Peak Detection

Chuang's algorithm [30] was implemented in order to detect peaks of systolic and diastolic blood pressure. The algorithm is based on the "findpeaks" function in MATLAB and focuses on three modifiable parameters: peak distance, peak height, and peak prominence. An illustration of these parameters is presented in Figure 5 (adapted from [30]). Owing to the variation in physiological conditions both between participants, and within a participant's own dataset, the algorithm was necessary to optimize blood pressure peak detection. Briefly, the dataset is split into 50 segments, and for each segment an automated approach is taken whereby the algorithm tests many different parameter settings for the "findpeaks" function to obtain the highest accuracy in detecting blood pressure peaks. Once the highest peak detection accuracy is obtained, the "findpeaks" function is run a final time with the optimal settings for that individual segment. Blood pressure peak locations and values are stored for later use. The algorithm then advances to the next BP data segment and repeats the process, finding a new set of optimal parameters for the new segment. Blood pressure is calculated during the 50 segments regardless of the number of respiratory events.

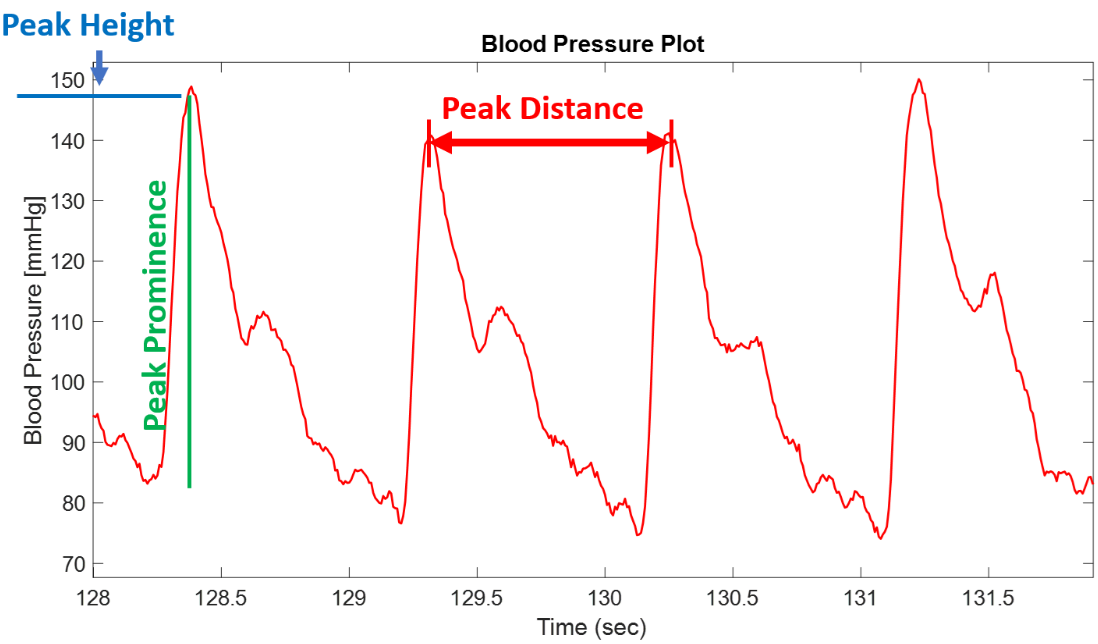

Figure 5 Illustration of key parameters in Chuang's algorithm [30]. Peak distance is defined as the temporal distance between two peaks. Peak height is simply the magnitude of a peak. Peak prominence is a relative parameter in MATLAB defined by the height of a peak compared to the peaks surrounding it.

The exact same algorithm also detects diastolic blood pressure peaks with a slight modification to the algorithm: as the "findpeaks" function explicitly only works with local maxima, one must invert the dataset so that systolic blood pressure values become local minima, and diastolic blood pressure become local maxima. Once this conversion is completed, the same algorithm is run on the inverted diastolic blood pressure data to find a separate set of optimal parameters for the diastolic BP peaks. Diastolic BP peak values and locations are stored for later use. The process is repeated for all 50 data segments.

2.4 Respiratory Events and Detection of Respiratory Event Chains

2.4.1 Respiratory Events

The principal types of respiratory events are as follows: obstructive sleep apnea (OSA), central apnea, mixed apnea and hypopnea. Hypopnea is defined as a partial obstruction of the upper airway [1]. Each of these respiratory event types can occur in isolation or in succession. Analyzing the impact of events occurring in rapid succession is one of the aims of this study. An isolated event is defined as any respiratory event, whether any type of apnea or hypopnea, that is farther than 30 seconds from all other events. A respiratory event chain (REC) is composed of any group of two or more respiratory events that have a recovery period of less than 30 seconds between them. Figure 6 illustrates two types of RECs: on the left side of 7000 seconds is a REC that contains multiple event types, referred to as an inhomogeneous respiratory event chain (IHREC). To the right of 7000 seconds is a REC that contains one event type (hypopnea), referred to as a homogenous respiratory event chain (HREC).

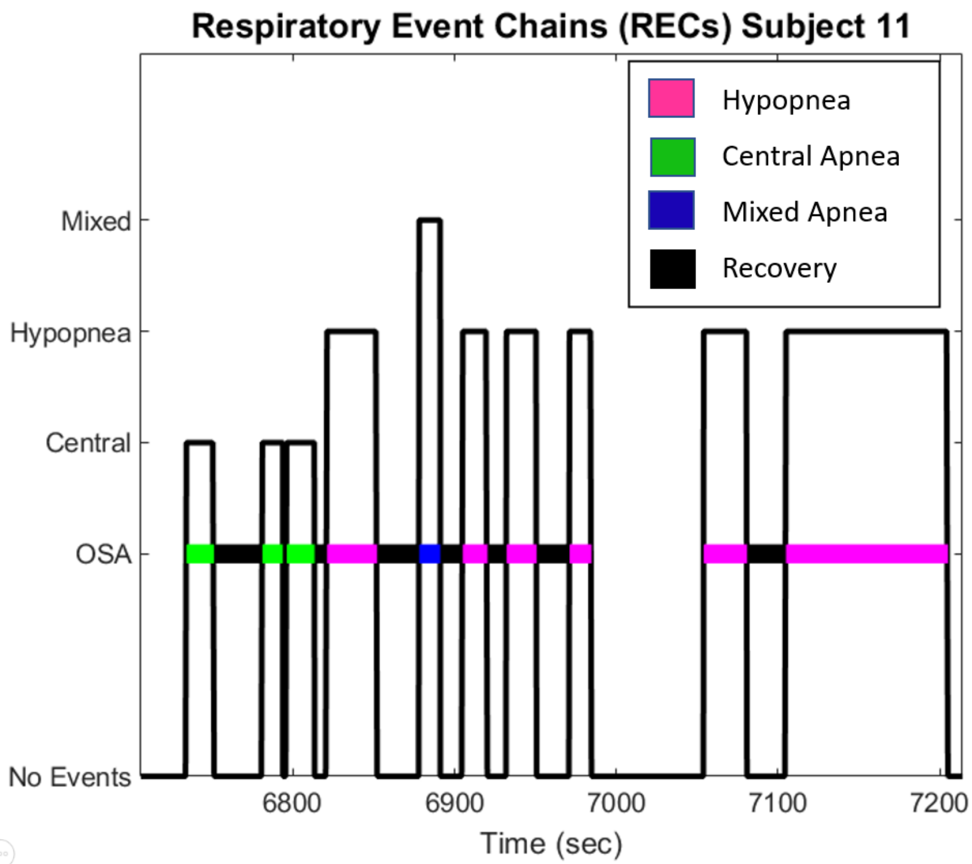

Figure 6 The two categories of RECs: homogeneous (right) and inhomogeneous (left). Recovery periods are denoted in black.

2.4.2 Detection of Respiratory Event Chains

To detect the RECs, a MATLAB algorithm was designed to scan through the nocturnal event marker data from the polysomnography. The algorithm logic for creating RECs as follows: given a set of event marker data, scan through the individual event markers in order, measuring the temporal distance between them. Repeat this process until the temporal distance between two event markers is less than 30 seconds apart. Once two or more event markers are identified with these criteria, stop searching and categorize these two events as an REC (Figure 7). Calculate the distance between the last event in the REC and the next event. If the distance is less than 30 seconds, consider this event as part of the current REC. Repeat the process for the next event, stopping when a gap greater than 30 seconds is identified (Figure 8). Once a gap greater than 30 seconds is identified between the last event in the REC and the next event, consider this REC complete and move on to the next event. Continue calculating the temporal distance between events until another REC is identified and repeat the previously mentioned steps.

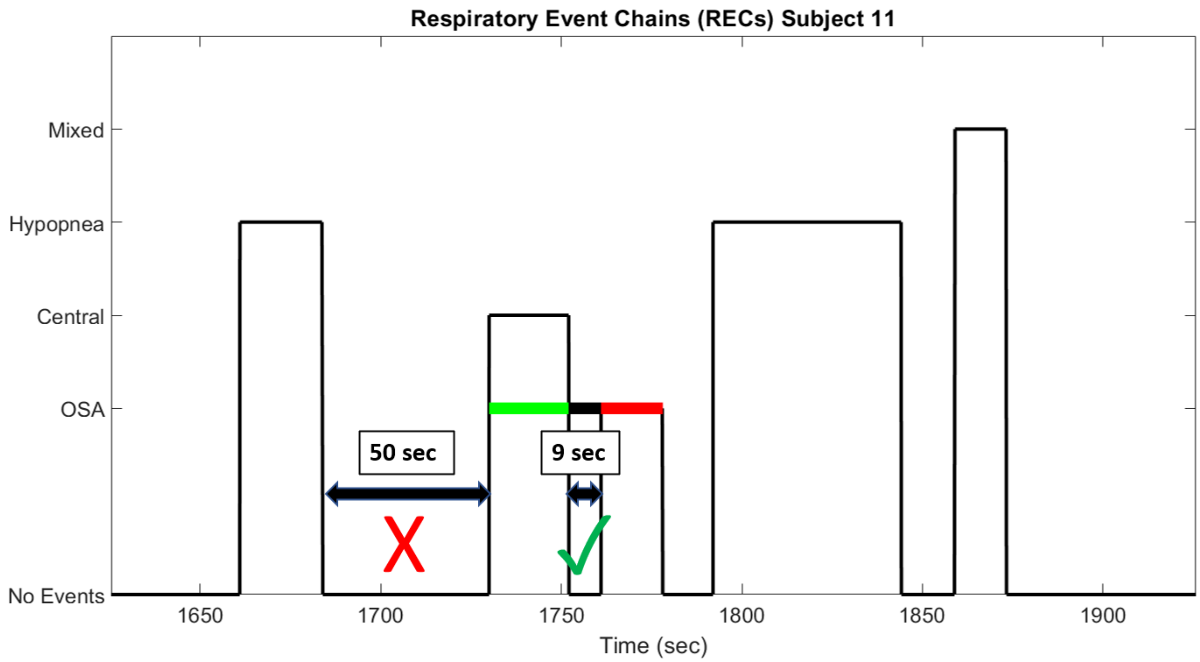

Figure 7 An illustration of detecting RECs. Events with a distance greater than 30 seconds are classified as isolated events. Those less than 30 seconds apart are grouped into RECs. The hypopnea to the left of 1700 seconds is an isolated event since it is greater than 30 seconds from any other event.

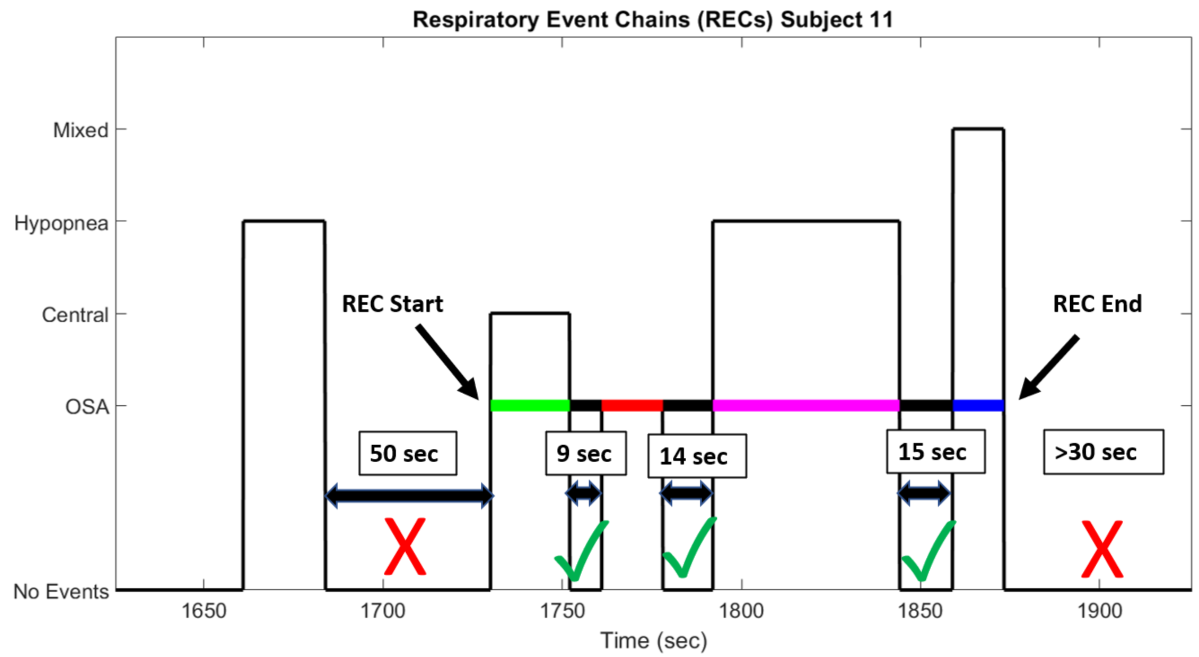

Figure 8 An illustration of RECs with multiple events. Respiratory events continue to be added to the REC until a gap greater than 30 seconds is identified.

For the purposes of quantifying the impact of SDB on blood pressure, 10 seconds of post-event BP data was included in event calculations (Figure 9). The inclusion of this 10 second period accounted for the blood pressure surge associated with the 5-7 seconds following an respiratory event as noted by Chuang [30] (Figure 10). For temporal event fraction ratio (TEFR) calculations, the 10 second inclusion of recovery was counted as part of the respiratory event (section 2.3.3.2). For events with a recovery period less than 10 seconds, the entire recovery period was included instead. When the recovery period was less than 10 seconds, this resulted in a TEFR of zero, as there is no leftover recovery period to consider in the calculations. An example of this phenomenon is illustrated by the recovery period following the central apnea in Figure 9.

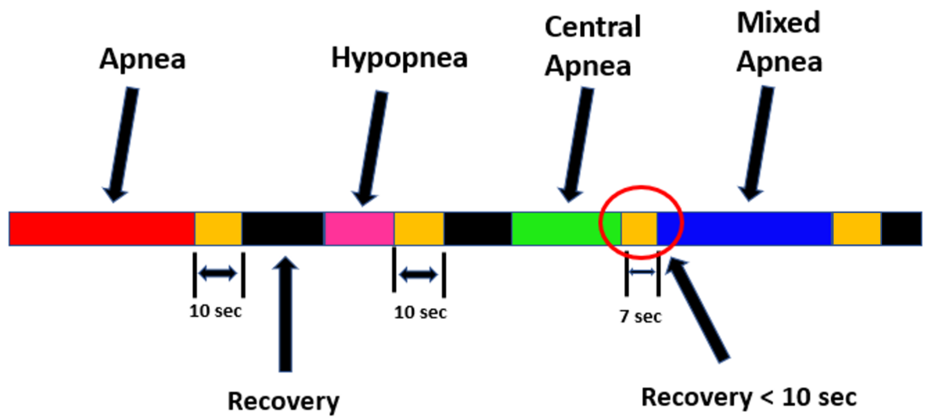

Figure 9 An illustration of inclusion of 10 seconds post-recovery for each event in a REC.

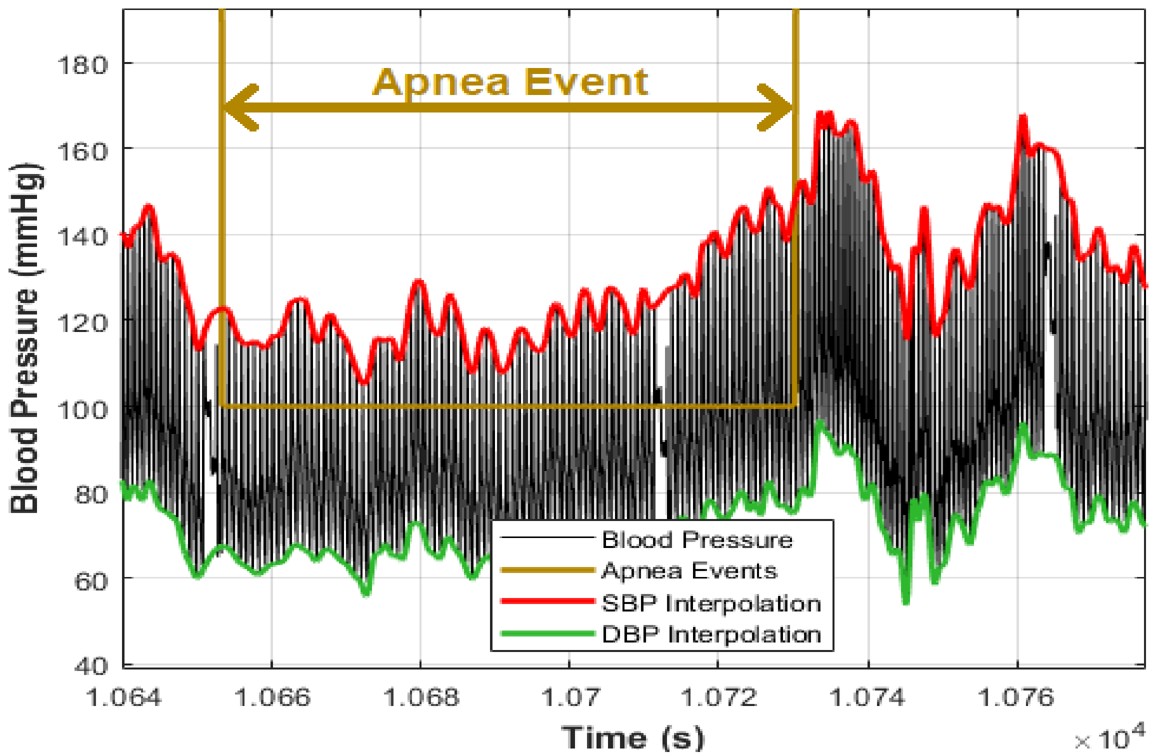

Figure 10 An example of blood pressure surge 5-7 seconds after an respiratory event. The yellow box denotes the beginning and end of an respiratory event. After the respiratory event ends, there is a clear rise in both systolic and diastolic blood pressure. Adapted from Chuang [30].

2.4.3 Cardiovascular Metrics

Rate pressure product (RPP) is defined as the product of heart rate and systolic blood pressure (SBP) [17]. Typically, rate pressure product is calculated over a specified duration of time, 1 minute, 5 minutes, etc. An instantaneous RPP (IRRP) was calculated using the instantaneous heart rate (IHR) obtained from using two consecutive heartbeats as detected from the blood pressure waveform. The equations for calculating IRPP are provided below:

$$IHR = \frac{1}{t} * 60 \qquad (2.1)$$

Where IHR is the instantaneous heartrate in beats per minute (bpm) and t represents the time in seconds between consecutive blood pressure peaks.

$$IRPP = IHR * SBP \qquad (2.2)$$

Where IRPP represents the instantaneous rate pressure product in units of mmHg*bpm and SBP represents systolic blood pressure.

An illustration of the metrics required for calculating IRPP is presented in Figure 11. The most recent SBP reading of the pair of blood pressure peaks which are used for computing the IHR is taken as the blood pressure. In Figure 11 the blood pressure value would be 113 mmHg. Instantaneous heart rate (IHR) is calculated by taking the temporal distance between each pair of peaks and converting it into heart rate in bpm. This IHR is then multiplied by the current systolic blood pressure resulting in an IRPP value for that set of peaks.

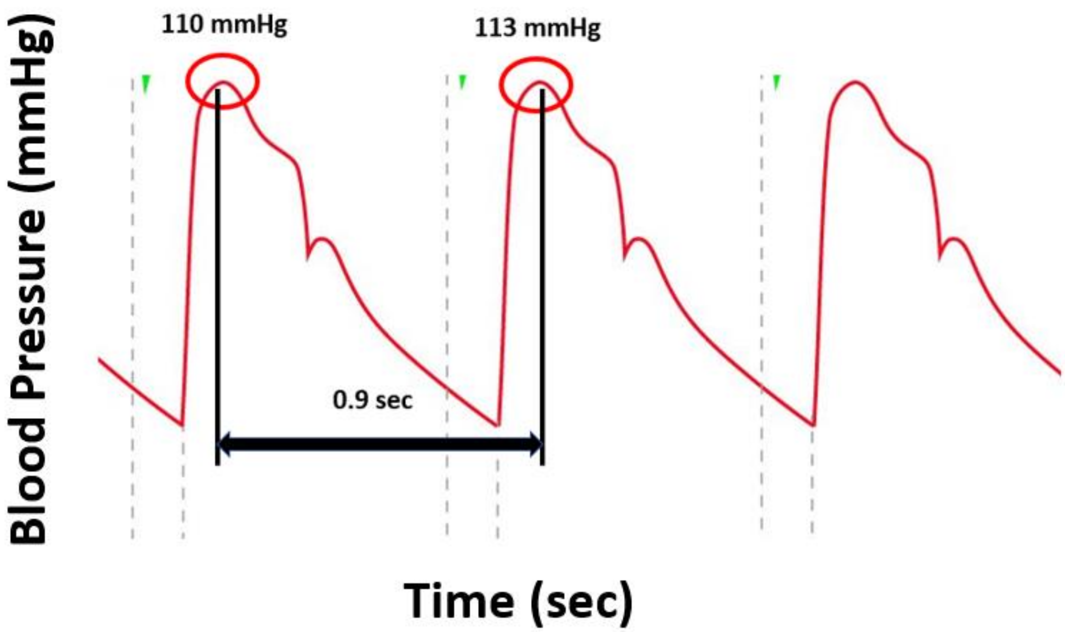

Figure 11 An illustration of metrics required to calculate instantaneous rate pressure product (IRPP). Using equation 2.1 and equation 2.2, IRPP values can be calculated for each set of peaks.

RPP is a reliable metric to quantify cardiac work and has been used in various research and clinical settings [32]. It is aimed that blood pressure surges caused by sleep apnea are effectively captured by deviations in RPP. Apart from its own utility, further metrics can be derived from RPP such as average energy, variance, and standard deviation. The RPP metrics of interest are outlined below.

2.4.3.1 Average Rate Pressure Product Energy

In signal processing, energy is defined as the sum of all squared values in a signal as presented in Equation 2.3. For finite signals, the energy is always finite [33]. This form of energy is distinct from the traditional definition of energy in physics.

$$\bar{E}(i) = \sum_{n=1}^{q} \frac{\lfloor IRPP(n) \rfloor^2}{qT} \qquad (2.3)$$

Where $\bar{E}(i)$ is the average energy of RPP for the event i, q is the number of heartbeats in event i, T is the sample interval and IRPP is defined according to equation 2.2.

In the context of RECs, the energy of the RPP was calculated within every event in a chain of respiratory events. As a result, each event within an REC would have a respective RPP energy value. The RPP energy calculation included the 10 second recovery period mentioned earlier. Figure 12 plots the RPP waveform for events in an REC. each event has its own RPP values which are all squared and summed together to give one RPP energy value for each event. By definition, the energy computation for a longer signal, or signal with more data points, will have a larger energy. To account for this phenomenon, each respiratory event RPP energy was normalized with respect to its event duration (i.e., qT was included in the denominator of equation 2.3) in seconds to obtain energy per unit time in $\frac{(mmHg)^2}{sec}$.

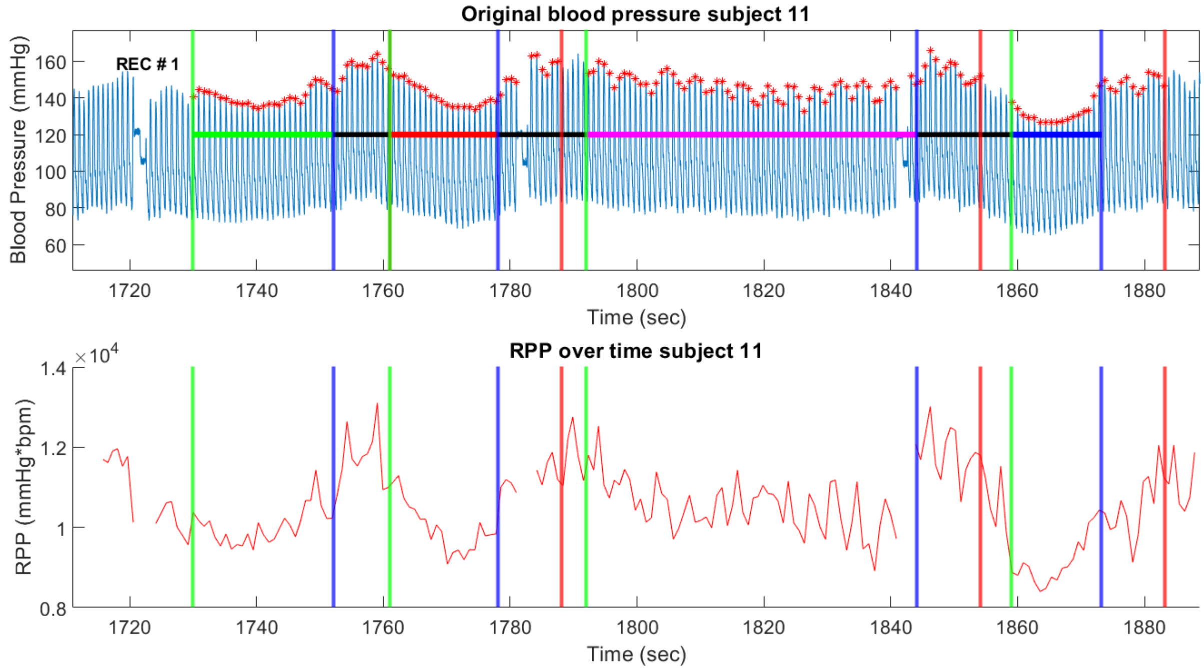

Figure 12 Temporally synchronized blood pressure and rate pressure product plots for subject 11, REC #1. Time ranges for RPP energy calculations are denoted by the colored vertical lines. Green lines represent the start of an event in the REC, blue lines the end of an event, and the red line the 10 second recovery inclusion (RI).

Once $\bar{E}(i)$ was obtained, the corresponding mean, variance, and standard deviation of $\bar{E}(i)$ for the entire event within the REC were calculated. These metrics were documented and plotted as well as used to conduct statistical tests. For isolated respiratory events, the same procedure was carried out for RPP energy calculations. This was possible due to the hierarchy of RPP calculations. To elaborate, even though each REC consists of multiple respiratory events, the calculations were still carried out with respect to each event as an individual unit. Each event provides associated statistical measures such as variance and mean of $\bar{E}(i)$. It is noted that the same procedure could be carried out for isolated events. However, as isolated events are not followed by any other respiratory events, the recovery periods for isolated events were always 10 seconds long, as opposed to RECs where a respiratory event would occasionally be rapidly followed by another event, thus making the recovery period less than 10 seconds (section 2.3.2).

A similar procedure was followed for calculating the mean and standard deviation of RPP. Normalization of mean RPP with respect to event length was computed for each individual event. A more mathematically detailed explanation of RPP energy, mean RPP, and other RPP related metrics can be found in section 2.3.3.3.

2.4.3.2 Temporal Event Fraction Ratio

Temporal event fraction ratio (TEFR) is the ratio of time spent in a respiratory event to the amount of recovery before the next event.

Every respiratory event is appended with a 10 second recovery period (Figure 13). As the 10 second recovery inclusion does not change, the TEFR depends on the respiratory event length (REL) and the remaining recovery period (RP) before the next event.

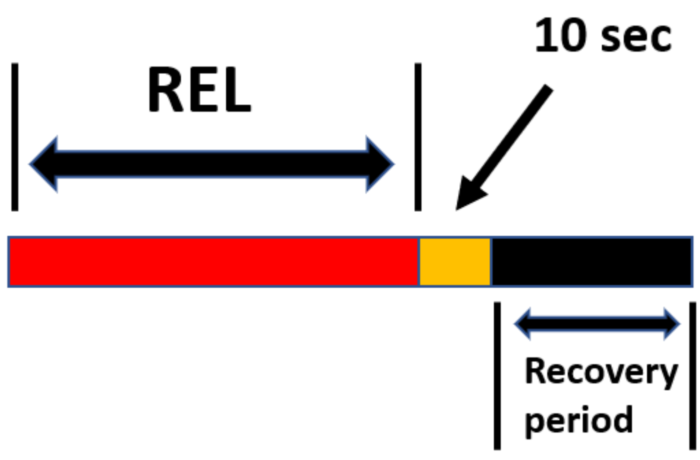

Figure 13 Illustration of variables for TEFR calculations

$$\text{Temporal Event Fraction Ratio} = \frac{REL + 10}{RP} \qquad (2.4)$$

Where REL represents the respiratory event length in seconds and RP represents the remaining recovery period before the next respiratory event.

Due to variability of duration and types of respiratory events in a REC, computation of RPP and other metrics requires additional consideration. For this purpose, a mathematical description is introduced which defines the possible key features of a REC and how calculations may be carried out. The concept is used to describe several other metrics in a consistent manner. An illustration of this computational structure is provided in Figure 14. From this point onward, event duration (ED) refers to the combined duration of a respiratory event and its recovery inclusion (RI).

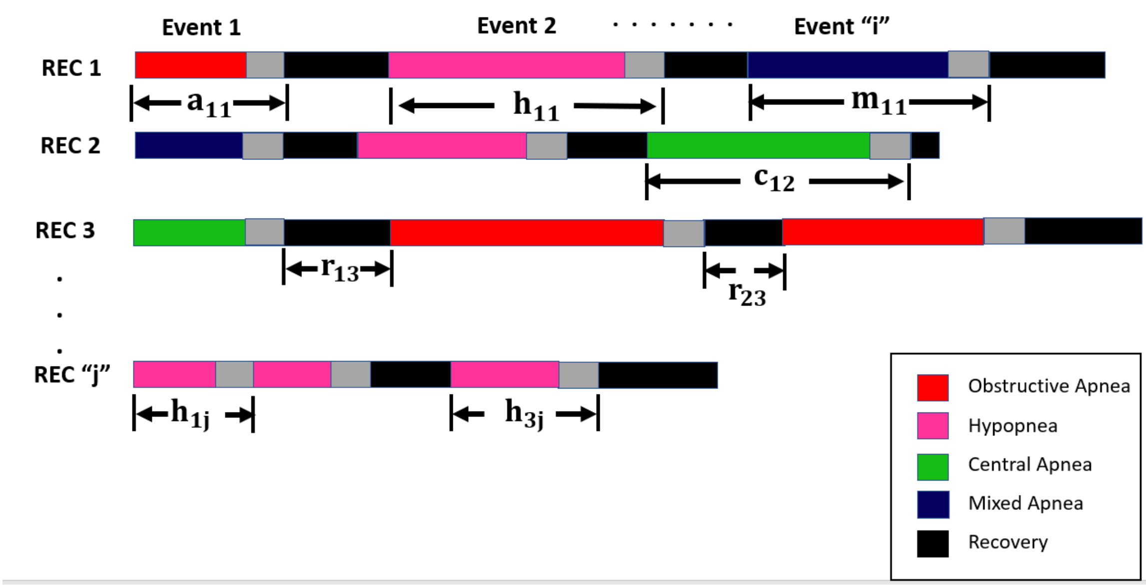

Figure 14 Schematic of mathematical procedure for conducting REC calculations. The concept can be applied to TEFR, RPP energy, and many other metrics.

Consider the following definitions:

a_{ij} : represent the event duration of an obstructive sleep apnea i occurring in REC j in seconds

na_j : represent the total number of obstructive respiratory events occurring in REC j

$h_{ij:}$ represent the event duration of a hypopnea i occurring in REC j in seconds

nh_j : represent the total number of hypopnea events occurring in REC j

c_{ij}: represent event duration of central apnea i occurring in REC j in seconds

nc_j : represent total number of central respiratory events occurring in REC j

m_{ij}: represent event duration of mixed apnea i occurring in REC j in seconds

nm_j : represent total number of mixed respiratory events occurring in REC j

r_{ij}: represent event duration of recovery period i occurring in REC j in seconds

nr_j : represent total number of recovery periods occurring in REC j

t_j: represent total duration of REC j in seconds

n_j: represent the total number of RECs

Thus, the total duration of REC j can be written as:

$$t_j = \sum_{i=1}^{na_j} \mathrm{a_{ij}} + \sum_{i=1}^{nh_j} \mathrm{h_{ij}} + \sum_{i=1}^{nc_j} \mathrm{c_{ij}} + \sum_{i=1}^{nm_j} \mathrm{m_{ij}} + \sum_{i=1}^{nr_j} \mathrm{r_{ij}} \qquad (2.5)$$

Recall that the event duration of each a_{ij} , h_{ij} etc. includes the 10 second inclusion into the recovery period. So, these 10 seconds are excluded from all r_{ij} durations.

Furthermore, the temporal event fraction ratio (TEFR) for each event type can be computed as:

$$TEFR_{aij} = \frac{a_{\text{ij}}}{r_{\text{ij}}} \qquad (2.6)$$

Where $TEFR_{aij}$ represents the TEFR of OSA i occurring in REC j

$$TEFR_{cij} = \frac{c_{\text{ij}}}{r_{\text{ij}}} \qquad (2.7)$$

Where $TEFR_{cij}$ represents the TEFR of central apnea i occurring in REC j

$$TEFR_{mij} = \frac{m_{\text{ij}}}{r_{\text{ij}}} \qquad (2.8)$$

Where $TEFR_{mij}$ represents the TEFR of mixed apnea i occurring in REC j

$$TEFR_{hij} = \frac{h_{\text{ij}}}{r_{\text{ij}}} \qquad (2.9)$$

Where $TEFR_{hij}$ represents the TEFR of hypopnea i occurring in REC j

The temporal event fraction ratio (TEFR) reflects the dominance of an event type in an REC. For the correlation analysis in Chapter 3 section 3.3, the TEFR for all events during each REC was averaged together to make one aggregate value for each REC. This averaging was done for three groups: 1) all respiratory event types, 2) OSA events and 3) hypopneas events.

2.4.3.3 computations for RPP metrics

Applying the previously described equations (2.3-2.9) to RPP, the following metrics were computed:

Let $aERPP_{\mathrm{ij}}$ be the rate pressure product energy of obstructive apnea (OSA) event i in REC j

The normalized mean RPP energy of OSA event i in REC j is:

$$\overline{aERPP}_{ijnorm} = \frac{\mathrm{aERPP_{ij}}}{\mathrm{a_{ij}}} \qquad (2.10)$$

The normalized mean RPP energy of all OSA events in REC j is:

$$\overline{aERPP}_{jnorm} = \frac{\sum_{i=1}^{na_j} \overline{aERPP}_{ijnorm}}{\mathrm{na_{ij}}} \qquad (2.11)$$

And the normalized mean OSA RPP energy of all RECs is:

$$\overline{aERPP}_{norm} = \frac{\sum_{j=1}^{n_j} \overline{aERPP}_{jnorm}}{n_j} \qquad (2.12)$$

Where n_j is the total number of RECs for the patient

Following the same procedure for the other event types:

$$\overline{cERPP}_{jnorm} = \frac{\sum_{i=1}^{nc_j} \overline{cERPP}_{ijnorm}}{\mathrm{nc_{ij}}} \qquad (2.13)$$

Where $\overline{cERPP}_{jnorm}$ is the normalized mean central apnea energy of all OSA events in REC j and $\overline{cERPP}_{ijnorm}$ is the normalized mean RPP energy of central apnea event i in REC j, and $\mathrm{nc_{ij}}$ is the total number of central apnea events in REC j.

$$\overline{cERPP}_{norm} = \frac{\sum_{j=1}^{j} \overline{cERPP}_{jnorm}}{n_j} \quad (2.14)$$

Where $\overline{cERPP}_{norm}$ is the normalized mean central apnea RPP energy of all RECs

$$\overline{mERPP}_{jnorm} = \frac{\sum_{i=1}^{nm_j} \overline{mERPP}_{ijnorm}}{\mathrm{nm}_{\mathrm{ij}}} \quad (2.15)$$

Where $\overline{mERPP}_{jnorm}$ is the normalized mean mixed apnea energy of all OSA events in REC j and $\overline{mERPP}_{ijnorm}$ is the normalized mean RPP energy of mixed apnea event i in REC j, and nm_{ij} is the total number of mixed apnea events in REC j.

$$\overline{mERPP}_{norm} = \frac{\sum_{j=1}^{j} \overline{mERPP}_{jnorm}}{n_j} \quad (2.16)$$

Where $\overline{mERPP}_{norm}$ is the normalized mean mixed apnea RPP energy of all RECs

$$\overline{hERPP}_{jnorm} = \frac{\sum_{i=1}^{nh_j} \overline{hERPP}_{ijnorm}}{\mathrm{nh}_{\mathrm{ij}}} \quad (2.17)$$

Where $\overline{hERPP}_{jnorm}$ is the normalized mean hypopnea energy of all hypopnea events in REC j and $\overline{hERPP}_{ijnorm}$ is the normalized mean RPP energy of hypopnea event i in REC j, and nh_{ij} is the total number of hypopnea events in REC j.

$$\overline{hERPP}_{norm} = \frac{\sum_{j=1}^{j} \overline{hERPP}_{jnorm}}{n_j} \quad (2.18)$$

Where $\overline{hERPP}_{norm}$ is the normalized hypopnea RPP energy of all RECs

$$\overline{ERPP}_{jnorm} = \frac{\sum_{i=1}^{na_j} \overline{aERPP}_{ijnorm} + \sum_{i=1}^{nc_j} \overline{cERPP}_{ijnorm} + \sum_{i=1}^{nm_j} \overline{mERPP}_{ijnorm} + \sum_{i=1}^{nh_j} \overline{hERPP}_{ijnorm}}{na_j + nc_j + nm_j + nh_j} \quad (2.19)$$

Where $\overline{ERPP}_{jnorm}$ is the total normalized RPP energy of REC j for all event types

And the mean RPP energy of all RECs for all event types is:

$$\frac{\sum_{j=1}^{n_j} \overline{ERPP}_{jnorm}}{n_j} \quad (2.20)$$

Let $\overline{aRPP_{\mathrm{kj}}}$ represent the mean rate pressure product of obstructive apnea (OSA) event k in REC j, then the mean rate pressure product of all OSA events occurring in all RECs is:

$$\overline{aRPP} = \frac{\sum_{k=1}^{l_j} \sum_{j=1}^{n_j} \overline{\mathrm{aRPP}}_{\mathrm{kj}}}{l_j\, n_j} \quad (2.21)$$

Where l_j is the number of apnea events in REC j and n_j is the number of RECs for the patient

For other event types:

$$\overline{cRPP} = \frac{\sum_{k=1}^{l_j} \sum_{j=1}^{n_j} \overline{\mathrm{cRPP}}_{\mathrm{kj}}}{l_j\, n_j} \quad (2.22)$$

Where $\overline{cRPP_{\mathrm{kj}}}$ is the mean rate pressure product of central apnea event k in REC j and $\overline{cRPP}$ is the mean rate pressure product of all central apnea events occurring in all RECs for the patient.

$$\overline{mRPP} = \frac{\sum_{k=1}^{l_j} \sum_{j=1}^{n_j} \overline{\mathrm{mRPP}}_{\mathrm{kj}}}{l_j \, n_j} \quad (2.23)$$

Where $\overline{mRPP_{\mathrm{kj}}}$ is the mean rate pressure product of mixed apnea event k in REC j and $\overline{mRPP}$ is the mean rate pressure product of all mixed apnea events occurring in all RECs for the patient.

$$\overline{hRPP} = \frac{\sum_{k=1}^{l_j} \sum_{j=1}^{n_j} \overline{\mathrm{hRPP}}_{\mathrm{kj}}}{l_j \, n_j} \quad (2.24)$$

Where $\overline{hRPP_{\mathrm{kj}}}$ is the mean rate pressure product of hypopnea event k in REC j and $\overline{hRPP}$ is the mean rate pressure product of all hypopnea events occurring in all RECs for the patient.

$$\overline{\mathrm{RPP}} = \frac{\sum_{i=1}^{nj} \overline{\mathrm{aRPP}}_{\mathrm{n}} + \sum_{i=1}^{nj} \overline{\mathrm{cRPP}}_{\mathrm{n}} + \sum_{i=1}^{nj} \overline{\mathrm{mRPP}}_{\mathrm{n}} + \sum_{i=1}^{nj} \overline{\mathrm{hRPP}}_{\mathrm{n}}}{n_j} \quad (2.25)$$

Where $\overline{\mathrm{RPP}}$ is the total mean RPP for all event types

2.4.3.4 Computations for Blood Pressure and Heart Rate

Consider the following definitions for blood pressure:

Let $\overline{aBP_{ij}}$ represent the mean systolic blood pressure (SBP) of OSA event i occurring in REC j

Then, the mean BP of all OSA events occurring in all RECs is:

$$\overline{aBP} = \frac{\sum_{j=1}^{nj} \sum_{i=1}^{qj} \overline{\mathrm{aBP}}_{\mathrm{ij}}}{n_j * q_j} \quad (2.26)$$

Where q_j is the number of apnea events in the jth REC and n_j the total number of RECs for the patient

Let $\overline{cBP_{ij}}$ represent the mean systolic blood pressure (SBP) of central apnea event i occurring in REC j

Then, the mean BP of all central apnea events occurring in all RECs is:

$$\overline{cBP} = \frac{\sum_{j=1}^{nj} \sum_{i=1}^{qj} \overline{\mathrm{cBP}}_{\mathrm{ij}}}{n_j * q_j} \qquad (2.27)$$

Where q_j is the number of central apnea events in the jth REC and n_j the total number of RECs for the patient

Let $\overline{mBP_{ij}}$ represent the mean systolic blood pressure (SBP) of mixed apnea event i occurring in REC j

Then, the mean BP of all mixed apnea events occurring in all RECs is:

$$\overline{mBP} = \frac{\sum_{j=1}^{nj} \sum_{i=1}^{qj} \overline{\mathrm{mBP}}_{\mathrm{ij}}}{n_j * q_j} \qquad (2.28)$$

Where q_j is the number of mixed apnea events in the jth REC and n_j the total number of RECs for the patient

Let $\overline{hBP_{ij}}$ represent the mean systolic blood pressure (SBP) of hypopnea event i occurring in REC j

Then, the mean BP of all hypopnea events occurring in all RECs is:

$$\overline{hBP} = \frac{\sum_{j=1}^{nj} \sum_{i=1}^{qj} \overline{\mathrm{hBP}}_{\mathrm{ij}}}{n_j * q_j} \qquad (2.29)$$

Where q_j is the number of hypopnea events in the jth REC and n_j the total number of RECs for the patient

for mean blood pressure across all events in RECs:

$$\overline{\mathrm{BP}} = \frac{\sum_{j=1}^{nj}\sum_{i=1}^{qj}\overline{\mathrm{aBP}}_{\mathrm{ij}} + \sum_{j=1}^{nj}\sum_{i=1}^{qj}\overline{\mathrm{cBP}}_{\mathrm{ij}} + \sum_{j=1}^{nj}\sum_{i=1}^{qj}\overline{\mathrm{mBP}}_{\mathrm{ij}} + \sum_{j=1}^{nj}\sum_{i=1}^{qj}\overline{\mathrm{hBP}}_{\mathrm{ij}}}{n_j} \tag{2.30}$$

Where n_j is the total number of RECs of all event types in the patient.

Consider the following definitions for heart rate:

Let $\overline{aHR_{ij}}$ represent the mean heart rate (HR) of OSA event i occurring in REC j

Then, the mean HR of all OSA events occurring in all RECs is:

$$\overline{aHR} = \frac{\sum_{j=1}^{nj}\sum_{i=1}^{qj}\overline{\mathrm{aHR}}_{\mathrm{ij}}}{n_j * q_j} \tag{2.31}$$

Let $\overline{cHR_{ij}}$ represent the mean heart rate (HR) of central apnea event i occurring in REC j

Then, the mean HR of all central apnea events occurring in all RECs is:

$$\overline{cHR} = \frac{\sum_{j=1}^{nj}\sum_{i=1}^{qj}\overline{\mathrm{cHR}}_{\mathrm{ij}}}{n_j * q_j} \tag{2.32}$$

Let $\overline{mHR_{ij}}$ represent the mean heart rate (HR) of mixed apnea event i occurring in REC j

Then, the mean HR of all mixed apnea events occurring in all RECs is:

$$\overline{mHR} = \frac{\sum_{j=1}^{nj}\sum_{i=1}^{qj}\overline{\mathrm{mHR}}_{\mathrm{ij}}}{n_j * q_j} \tag{2.33}$$

Let $\overline{hHR_{ij}}$ represent the mean heart rate (HR) of hypopnea event i occurring in REC j

Then, the mean HR of all hypopnea events occurring in all RECs is:

$$\overline{hHR} = \frac{\sum_{j=1}^{nj}\sum_{i=1}^{qj}\overline{\mathrm{hHR}}_{\mathrm{ij}}}{n_j * q_j} \qquad (2.34)$$

$$\overline{\mathrm{HR}} = \frac{\sum_{j=1}^{nj}\sum_{i=1}^{qj}\overline{\mathrm{aHR}}_{\mathrm{ij}} + \sum_{j=1}^{nj}\sum_{i=1}^{qj}\overline{\mathrm{cHR}}_{\mathrm{ij}} + \sum_{j=1}^{nj}\sum_{i=1}^{qj}\overline{\mathrm{mHR}}_{\mathrm{ij}} + \sum_{j=1}^{nj}\sum_{i=1}^{qj}\overline{\mathrm{hHR}}_{\mathrm{ij}}}{n_j} \qquad (2.35)$$

Where $\overline{\mathrm{HR}}$ represents the mean heart rate across all RECs for all event types

2.4.4 Statistical Analysis

Statistical analysis of metrics for REC & isolated events were conducted. For isolated events, paired two-tailed t-tests with an alpha level of 0.05 were conducted on both mean and standard deviation for RPP, RPP standard deviation, blood pressure, and heart rate across all subjects to determine if statistically significant differences existed. Also, comparisons were made for apnea and hypopnea events. For RECs, paired two-tailed t-tests ($\alpha = 0.05$) on the same metrics were conducted across all subjects to test for significant differences in mean or standard deviation. For RECs, correlation analysis was conducted to detect any significant trends in mean RPP energy and variance with respect to temporal event fraction ratio (TEFR). Regarding event-specific analysis, due to limited data for mixed and central apnea, the event-specific analysis was only conducted for apnea and hypopnea events.

CHAPTER 3

RESULTS

The results are divided into three main sections: 1) An analysis of RECs and isolated events with regards to the individual components of RPP: blood pressure and heart rate. 2) a subject-to-subject investigation of the differences of rate pressure product (RPP) metrics between respiratory event chains (RECs) and isolated events. And 3), the influence of REC duration and composition on the RPP.

3.1 Analysis of Blood Pressure and Heart Rate

As previously mentioned, RPP is a function of systolic blood pressure (SBP) and heart rate (HR). The following analysis was conducted to identify the contributions of SBP and HR to RPP, as well as investigate possible trends for RPP during various respiratory events.

Blood pressure and heart rate metrics were computed including the 10second recovery period following each event as described in section 2.3.3.4. Table 3 presents the results of blood pressure comparison between RECs and isolated respiratory events. The term "average" refers to the averaging of all RECs in a subject (irrespective of event type), as well as the averaging of all isolated events in a subject (irrespective of event type). For average SBP (Table 3 columns 2 & 3), the p-value was 0.801. For SBP standard deviation (columns 5 & 6), the p-value was 0.070. A plot of the average BP data in Table 3 is given in Figure 15.

Figure 16 contains box and scatterplots for the mean BP during each REC event in all subjects. The values in these REC scatter plots were used to compute column 2 in Table 3. Figure 17 provides similar box and scatter data for isolated events in all subjects. The values in these isolated event scatter plots were used to compute column 3 in Table 3.

Table 3 Comparison of Systolic Blood Pressure Metrics

Col. 1	**Col. 2**	**Col. 3**	**Col. 4**	**Col. 5**	**Col. 6**	**Col. 7**	**Col. 8**	**Col. 9**
Subject	**Average REC SBP (mmHg)**	**Average Isolated Event SBP (mmHg)**	**Difference (mmHg)**	**Average REC SBP Standard Deviation (mmHg)**	**Average Isolated BP Standard Deviation (mmHg)**	**Difference (mmHg)**	**Total # of REC Events**	**Total # of Isolated Events**
1	132	130	-2	6	8	1	10	24
2	109	110	1	5	6	0	176	66
3	144	146	2	7	7	0	103	27
4	127	129	3	11	11	1	38	59
5	117	117	0	10	7	-3	284	20
6	131	132	1	9	7	-2	130	11
7	145	150	5	12	7	-5	692	6
8	139	138	-1	8	7	-1	119	38
9	131	121	-10	10	9	-1	162	8
10	136	135	-1	13	7	-7	173	10
11	117	118	1	10	8	-2	185	53
12	124	120	-4	10	10	1	258	36
13	155	158	2	9	8	0	60	76
Mean ± SD	131 ± 13	131 ± 14	0 ± 4	9 ± 2	8 ± 2	-1 ± 2	184 ± 172	33 ± 24
T test	p = 0.80		---	p = 0.07		---	---	---

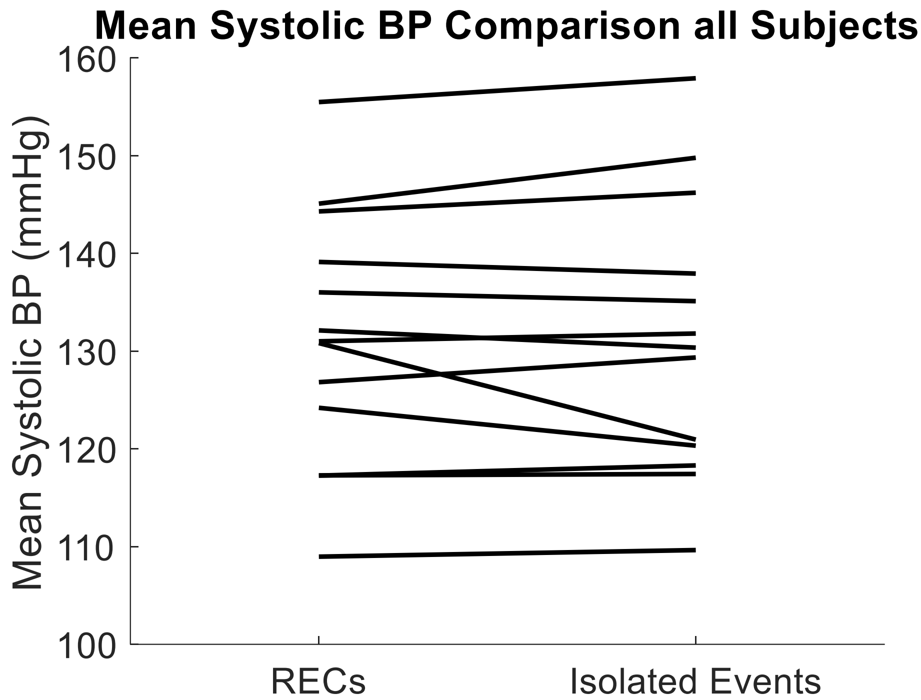

Figure 15 Line plot of mean systolic blood pressure between RECs and isolated events.

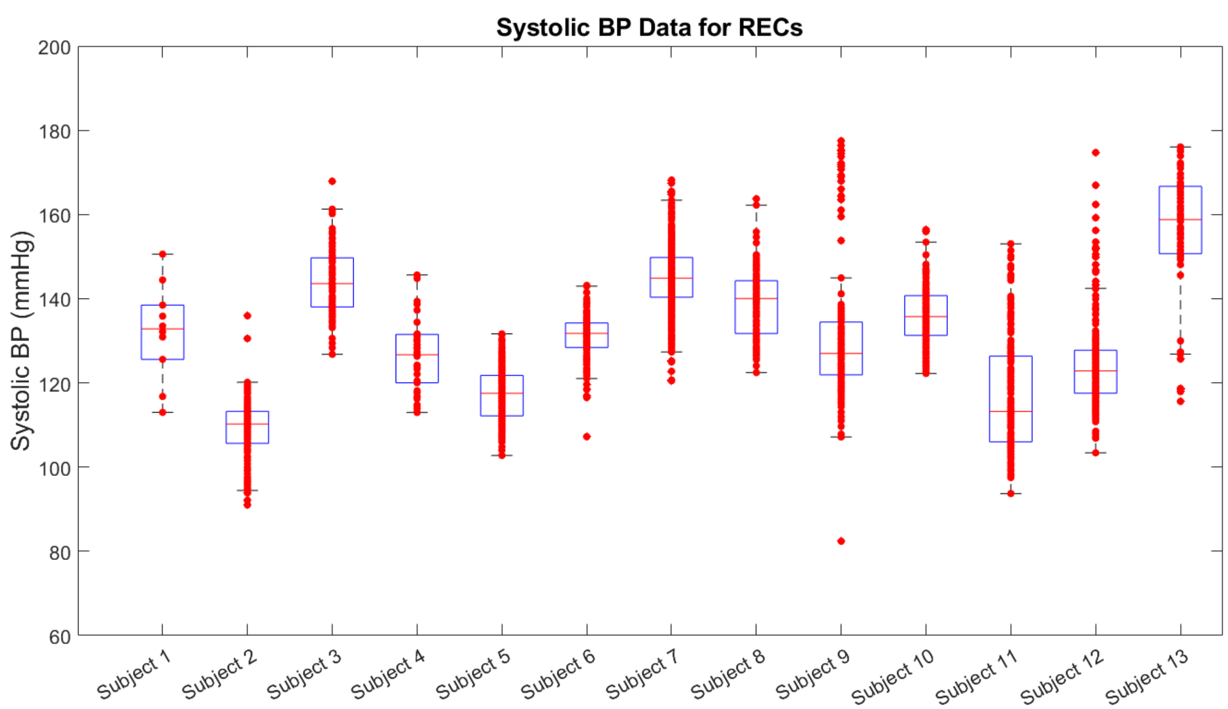

Figure 16 Box and scatterplot for mean systolic BP during RECs for all event types. The scatter values were used to compute column 2 of Table 3.

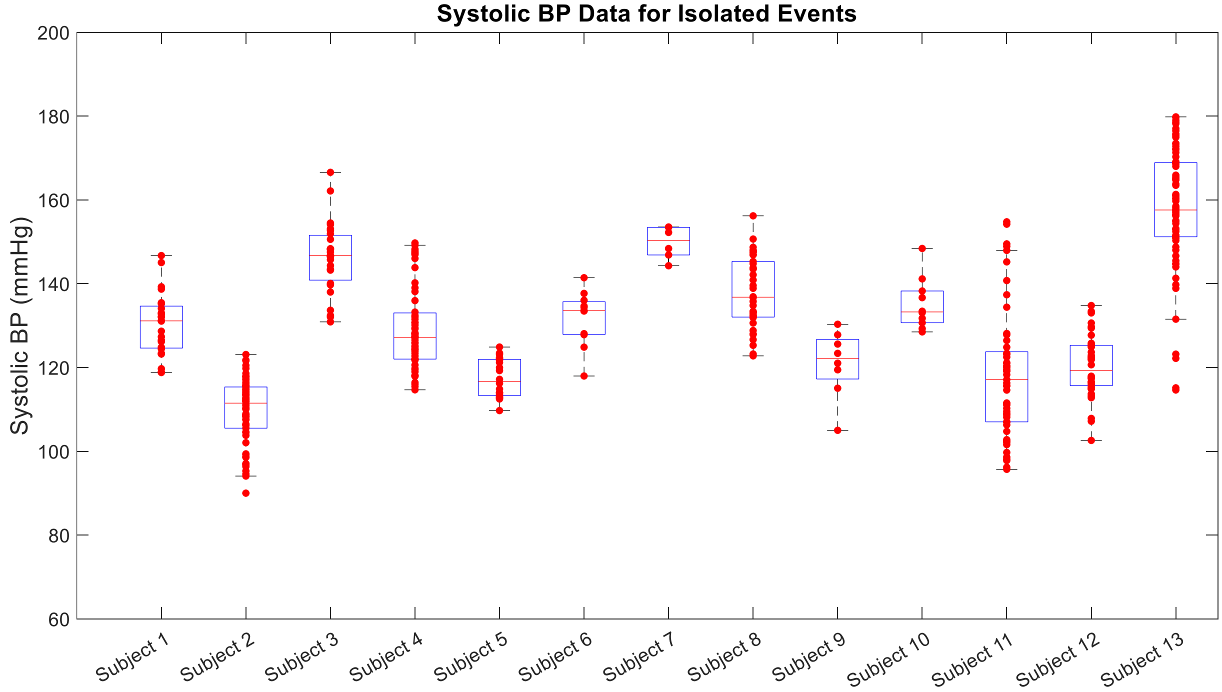

Figure 17 Box and scatterplot for mean systolic BP during isolated events for all event types. The scatter values were used to compute column 3 of Table 3.

Table 4 presents the results of heart rate analysis during RECs and isolated events. Figure 18 contains box and scatterplots for the mean HR during each REC event in all subjects. The values in these REC scatter plots were used to compute column 2 in Table 4. Figure 19 provides similar box and scatter data for isolated events in all subjects. The values in these isolated event scatter plots were used to compute column 3 in Table 4.

The average HR comparison (columns 2 & 3) resulted in a p-value of 0.220. The HR standard deviation comparison (columns 5 & 6) resulted in a p-value of 0.363. Figure 20 illustrates the average HR data from Table 4 as a line plot.

Table 4 Comparison of Heart Rate Metrics

Col. 1 Subject	Col. 2 Average REC HR (bpm)	Col. 3 Average Isolated Event HR (bpm)	Col. 4 Difference (bpm)	Col. 5 Average REC HR Standard Deviation (bpm)	Col. 6 Average Isolated HR Standard Deviation (bpm)	Col. 7 Difference (bpm)	Col. 8 Total # of REC Events	Col. 9 Total # of Isolated Events
1	59	60	1	5	5	0	10	24
2	75	75	0	3	3	0	176	66
3	52	53	1	4	4	0	103	27
4	54	52	-2	8	7	-1	38	59
5	68	68	0	4	3	-1	284	20
6	72	74	2	6	5	-1	130	11
7	82	83	0	3	3	-1	692	6
8	64	64	-1	2	2	0	119	38
9	73	75	2	4	5	1	162	8
10	47	49	2	4	2	-2	173	10
11	80	80	0	5	4	-1	185	53
12	81	79	-1	6	8	2	258	36
13	68	69	1	5	4	0	60	76
Mean ± SD	67 ± 12	68 ± 11	0 ± 1	5 ± 1	4 ± 2	0 ± 1	184 ± 172	33 ± 24
T test	p = 0.22		---	p = 0.36		---	---	---

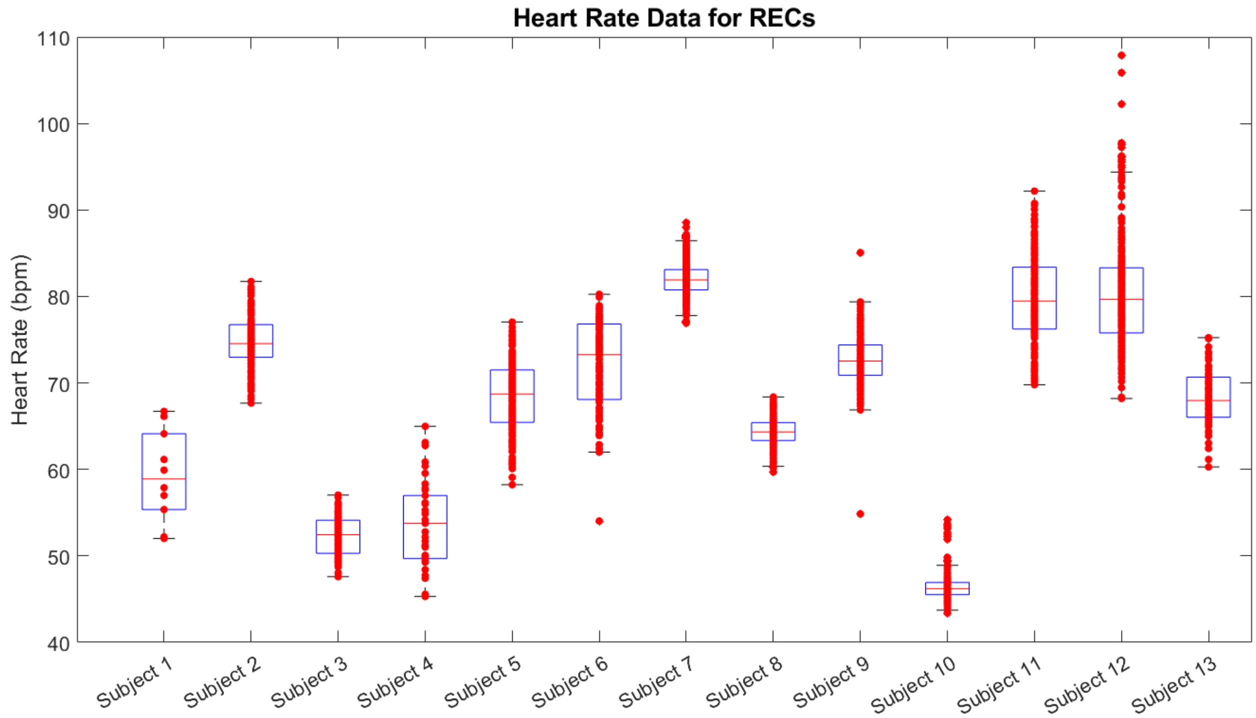

Figure 18 Box and scatterplot for mean HR during RECs for all event types. The scatter values were used to compute column 2 of Table 4.

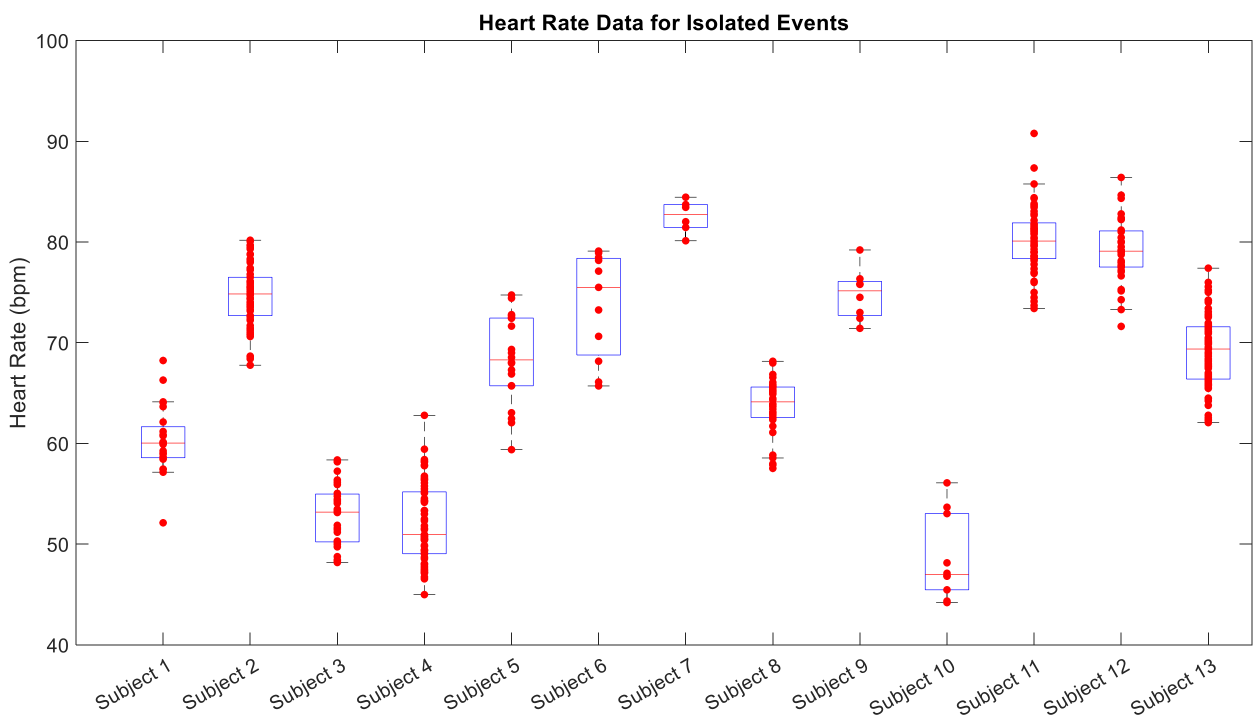

Figure 19 Box and scatterplot for mean HR during isolated events for all event types. The scatter values were used to compute column 3 of Table 4.

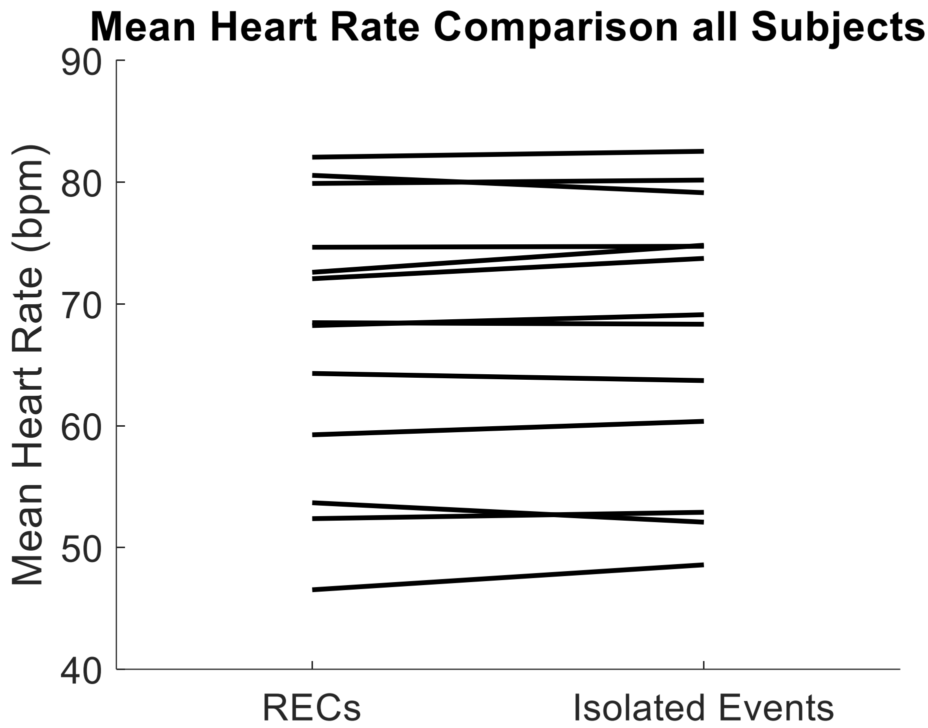

Figure 20 Line plot of mean heart rate between RECs and isolated events

3.2 Comparison of Rate Pressure Product

This section focuses on the comparison of normalized, averaged RPP metrics for events occurring during RECs, and those occurring during isolated respiratory events. A detailed procedure for the averaging of RPP metrics, as well as normalization of metrics, can be found in section 2.3.3.

Table 5 contains the average RPP computed during a 5-minute period of N1 sleep with no apnea events. These values serve as a baseline for RPP during respiratory events. Table 6 shows a comparison of RPP sample mean values and average of RPP standard deviation for two groups: RECs and isolated respiratory events. All event types are included in this table: obstructive apneas, central apneas, mixed apneas, and hypopneas. The term "average" in Table 6 refers to the averaging of all the RPP values in each respiratory event as described in section 2.3.3. Figure 21 contains box and scatterplots for the mean RPP during each event occurring in RECs. The values in these REC scatter plots were used to compute the entries in column 2 in Table 6. Figure 22 provides box and scatter data for isolated events in all subjects. The values shown in these isolated scatter plots were used to compute entries in column 3 in Table 6. Table 7 and Table 8 are constructed from the same data sets as Table 6, except only OSA and hypopnea events are considered. Figure 23 provides an illustration of this mixed distribution in mean RPP. Figure 24 contains a line plot of average RPP standard deviation between RECs and isolated events for all subjects. Neither RPP mean nor standard deviation for isolated events vs RECs differed significantly between the two conditions, although REC SD tended to exceed isolated event SD ($p > 0.07$; Table 6).

Table 5 Baseline RPP during N1 sleep with no respiratory events

Subject	Baseline RPP (mmHg*bpm)
1	---
2	6804 ± 378
3	8391 ± 585
4	5288 ± 491
5	7907 ± 590
6	10585 ± 636
7	14153 ± 1032
8	7921 ± 632
9	9299 ± 478
10	---
11	9114 ± 846
12	---
13	10180 ± 1003

Table 6 Rate Pressure Product Comparison - All Event Types

Col. 1	Col. 2	Col. 3	Col. 4	Col. 5	Col. 6	Col. 7	Col. 8	Col. 9
Subject	**Average REC RPP (mmHg*bpm)**	**Average Isolated Event RPP (mmHg*bpm)**	**Percent Change (%)**	**Average REC RPP Standard Deviation (mmHg*bpm)**	**Average Isolated RPP Standard Deviation (mmHg*bpm)**	**Percent Change (%)**	**Total # of REC Events**	**Total # of Isolated Events**
1	7841	7869	0.4	837	810	-3.2	50	37
2	8136	8193	0.7	577	614	6.4	197	66
3	7579	7771	2.5	878	909	3.5	108	29
4	6878	6795	-1.2	1416	1414	-0.1	42	59
5	8067	8047	-0.2	1056	742	-29.7	292	21
6	9461	9730	2.8	1154	966	-16.3	266	15
7	11925	12368	3.7	1295	805	-37.8	692	6
8	8952	8787	-1.8	737	685	-7.1	119	38
9	9522	9054	-4.9	1024	1061	3.7	466	28
10	6378	6566	2.9	1066	493	-53.7	321	18
11	9373	9478	1.1	1168	924	-20.9	186	54
12	10089	9571	-5.1	1268	1491	17.6	320	37
13	10646	10950	2.9	1112	1046	-5.9	64	77
Mean ± SD	8834 ± 1557	8860 ± 1611	0.3 ± 2.91	1045.2 ± 236	920 ± 288	-11 ± 20	184 ± 172	33 ± 24
T test	p = 0.75		---	p = 0.07		---	---	---

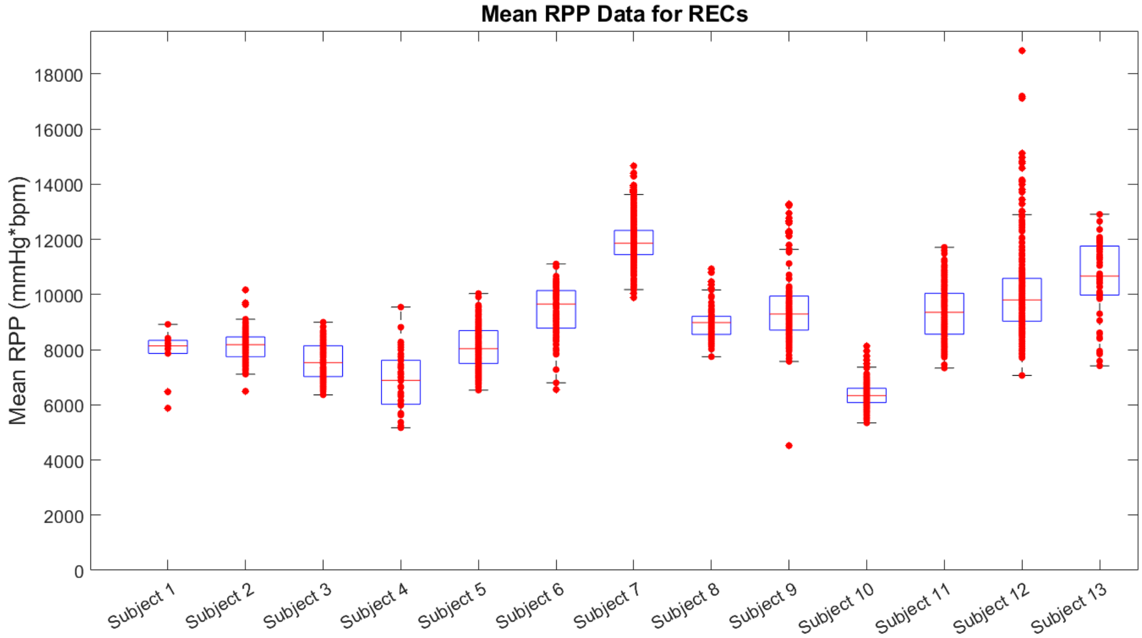

Figure 21 Box and scatterplot for mean RPP during REC events for all subjects. The scatter values for each subject shown in this figure were used to compute the corresponding entries in column 2 of Table 6.

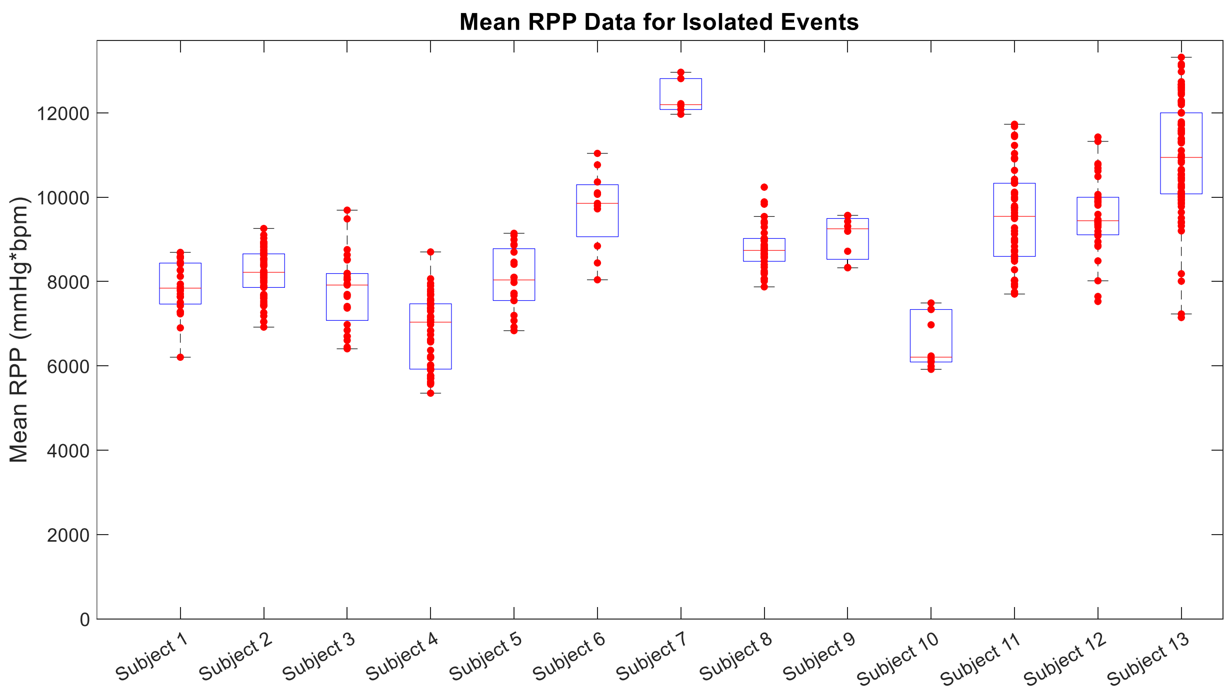

Figure 22 Box and scatterplot for mean RPP during REC events for all subjects. The scatter values for each subject were used to compute column 3 of Table 6.

Table 7 Rate Pressure Product Comparison - Obstructive Sleep Apnea

Col. 1	Col. 2	Col. 3	Col. 4	Col. 5	Col. 6	Col. 7	Col. 8	Col. 9
Subject	**Average REC RPP (mmHg*bpm)**	**Average Isolated Event RPP (mmHg*bpm)**	**Percent Change (%)**	**Average REC RPP Standard Deviation (mmHg*bpm)**	**Average Isolated RPP Standard Deviation (mmHg*bpm)**	**Percent Change (%)**	**# of OSA REC Events**	**# of Isolated OSA Events**
1	---	---	---	---	---	---	0	0
2	8198	8094	-1.3	687	895	30.3	21	8
3							40	0
4	7080	6710	-5.2	1733	1604	-7.4	18	20
5	8116	8101	-0.2	1166	901	-22.7	200	9
6	9605	9989	4.0	1127	877	-22.2	98	3
7	11993	12390	3.3	1269	802	-36.8	455	2
8	9459	9401	-0.6	956	755	-21.1	7	2
9	9561	9133	-4.5	1063	1188	11.8	132	6
10	6395	6439	0.7	1093	579	-47.1	148	3
11	9879	11227	13.6	1220	1028	-15.7	12	1
12	10273	10017	-2.5	1322	1773	34.1	181	16
13	10088	10718	6.2	941	855	-9.2	14	12
Mean ± SD	9150 ± 1584	9293 ± 1846	1.2 ± 5.4	1143 ± 264	1023 ± 364	-9.7 ± 25.7	102 ± 128	6 ± 6
T test	p = 0.38		---	p = 0.19		---	---	---

Table 8 Rate Pressure Product Comparison – Hypopnea

Col. 1	Col. 2	Col. 3	Col. 4	Col. 5	Col. 6	Col. 7	Col. 8	Col. 9
Subject	**Average REC RPP (mmHg*bpm)**	**Average Isolated Event RPP (mmHg*bpm)**	**Percent Change (%)**	**Average REC RPP Standard Deviation (mmHg*bpm)**	**Average Isolated RPP Standard Deviation (mmHg*bpm)**	**Percent Change (%)**	**# of Hypopnea REC Events**	**# of Isolated Hypopnea Events**
1	7839	7908	0.9	888	800	-9.8	9	22
2	8127	8207	1.0	562	575	2.3	155	58
3	7452	7818	4.9	886	903	1.9	62	25
4	6697	6839	2.1	1131	1317	16.5	20	39
5	8202	8084	-1.4	633	610	-3.6	48	10
6	9132	9633	5.5	1172	999	-14.8	17	8
7	12487	12963	3.8	835	650	-22.2	46	1
8	8920	8753	-1.9	724	681	-5.9	112	36
9	9347	8817	-5.7	845	681	-19.4	29	2
10	6290	6738	7.1	578	478	-17.3	10	6
11	9275	9339	0.7	1188	930	-21.7	158	48
12	9649	9147	-5.2	1127	1225	8.7	72	19
13	10816	11008	1.8	1164	1071	-8.0	46	63
Mean ± SD	8787 ± 1666	8866 ± 1683	1 ± 3.9	902 ± 234	840 ± 260	-7.1 ± 12.1	60 ± 51	26 ± 21
T test	p = 0.42		---	0.09		---	---	---

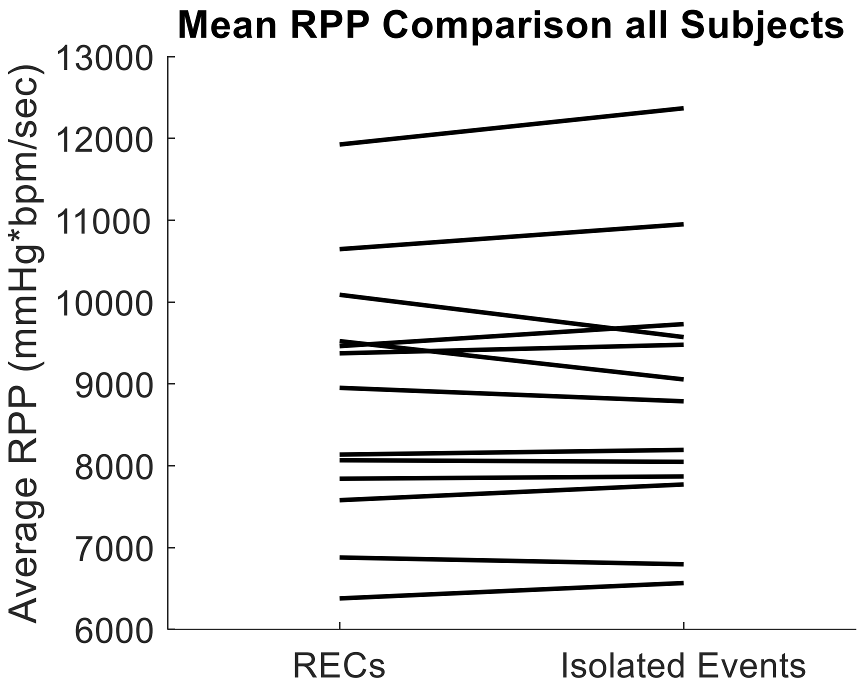

Figure 23 Comparison of mean RPP between RECs and isolated events for all subjects.

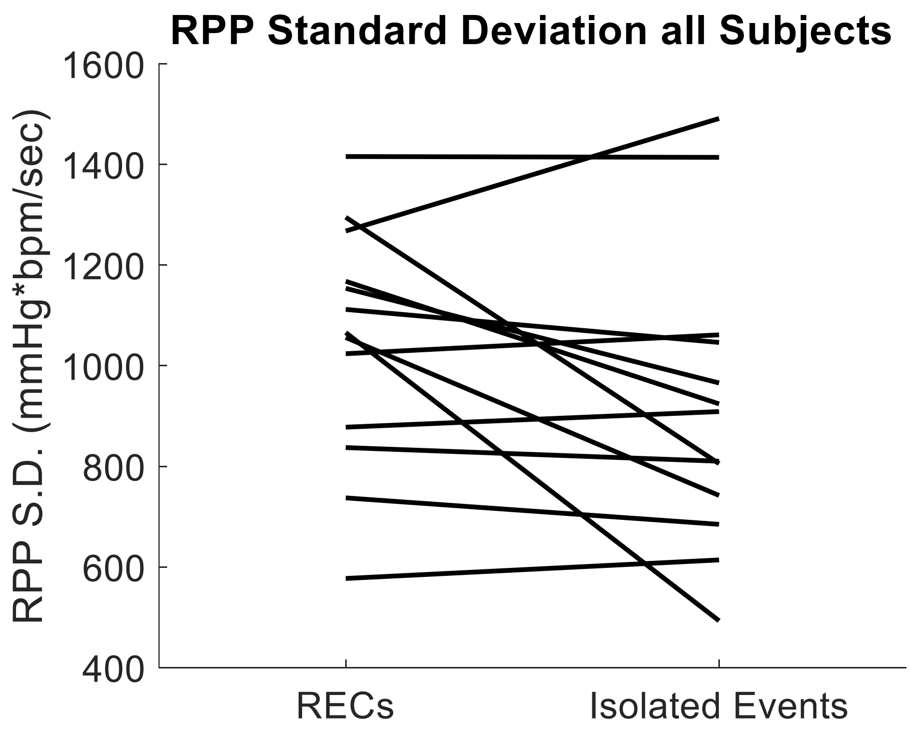

Figure 24 Comparison of RPP standard deviation between RECs and isolated events for all subjects.

Paired t-tests were conducted between the baseline RPP in Table 5, and the REC and isolated respiratory events in Table 6-Table 8. The comparisons were not statistically significant.

The normalized energy of RPP, as computed in 2.3.3 (i.e., RPP energy per second), was explored as a possible metric to complement the results of RPP. RPP energy results are found in Table 9. The t-test for columns 2 & 3 yielded a p-value of 0.62. Columns 5 and 6 contain the sample sizes for RECs and isolated events identified for each subject. For most metrics, each event within RECs was considered an individual data point for statistical analysis. The mean RPP, RPP standard deviation, etc. were computed with respect to the individual events in the RECs. However, the REC RPP energy was computed using all the events within a REC as one aggregate value. To elaborate, the mean RPP energy was computed by first averaging the normalized energy of all events within a REC to obtain one aggregate value for that REC. Afterwards, all the aggregate values for RECs were averaged once more to obtain one RPP energy metric for the entire subject. The same procedure for RPP energy was used to compute the RPP variance.

Figure 25 contains box and scatterplots for the normalized mean RPP energy during each REC in all subjects. The values in these REC scatter plots were used to compute column 2 in Table 9. Figure 26 provides similar box and scatter data for isolated events in all subjects. The values in these isolated event scatter plots were used to compute column 3 in Table 9.

Table 10 and Table 11 are constructed from the same data sets as Table 6, except only OSA and hypopnea events are considered. The p-value for mean RPP energy comparison in OSA events (Table 10 columns 2 & 3) was 0.174. The p-value for mean RPP energy comparison in hypopnea events (Table 11 columns 2 & 3) was 0.657.

Table 9 Comparison of Normalized Rate Pressure Product Energy – All Event Types

Col. 1	**Col. 2**	**Col. 3**	**Col. 4**	**Col. 5**	**Col. 6**
Subject	**Mean REC RPP Energy** $(\mathbf{mmHg} * \mathbf{bpm})^2/s$	**Mean Isolated RPP Energy** $(\mathbf{mmHg} * \mathbf{bpm})^2/s$	**Percent Change (%)**	**# of RECs**	**# of Isolated Events**
1	5.79E+07	5.72E+07	-1.21	5	24
2	7.52E+07	7.73E+07	2.77	48	66
3	4.39E+07	4.85E+07	10.49	22	27
4	3.98E+07	3.78E+07	-5.10	14	59
5	7.43E+07	6.94E+07	-6.65	52	20
6	9.27E+07	9.15E+07	-1.30	15	11
7	1.84E+08	1.97E+08	7.13	51	6
8	7.95E+07	7.77E+07	-2.26	32	38
9	9.36E+07	8.87E+07	-5.19	30	8
10	2.53E+07	2.94E+07	15.97	18	10
11	1.09E+08	1.13E+08	3.78	53	53
12	1.19E+08	1.12E+08	-5.76	41	36
13	1.22E+08	1.26E+08	3.64	25	76
Mean ± SD	8.59E+07 ± 4.21E+07	8.66E+07 ± 4.43E+07	1.25 ± 6.89	31 ± 16	33 ± 24
T test	p = 0.62		---	---	---

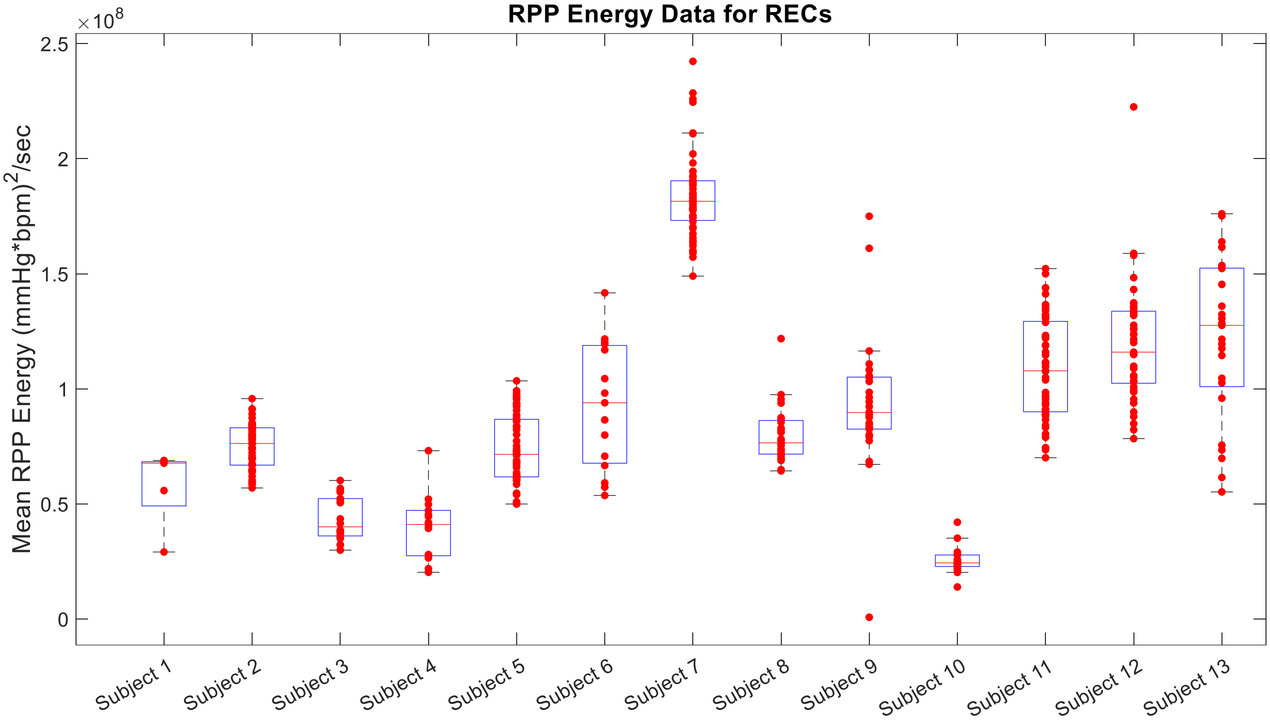

Figure 25 Box and scatterplot for normalized RPP energy during RECs for all event types. The scatter values were used to compute column 2 of Table 9.

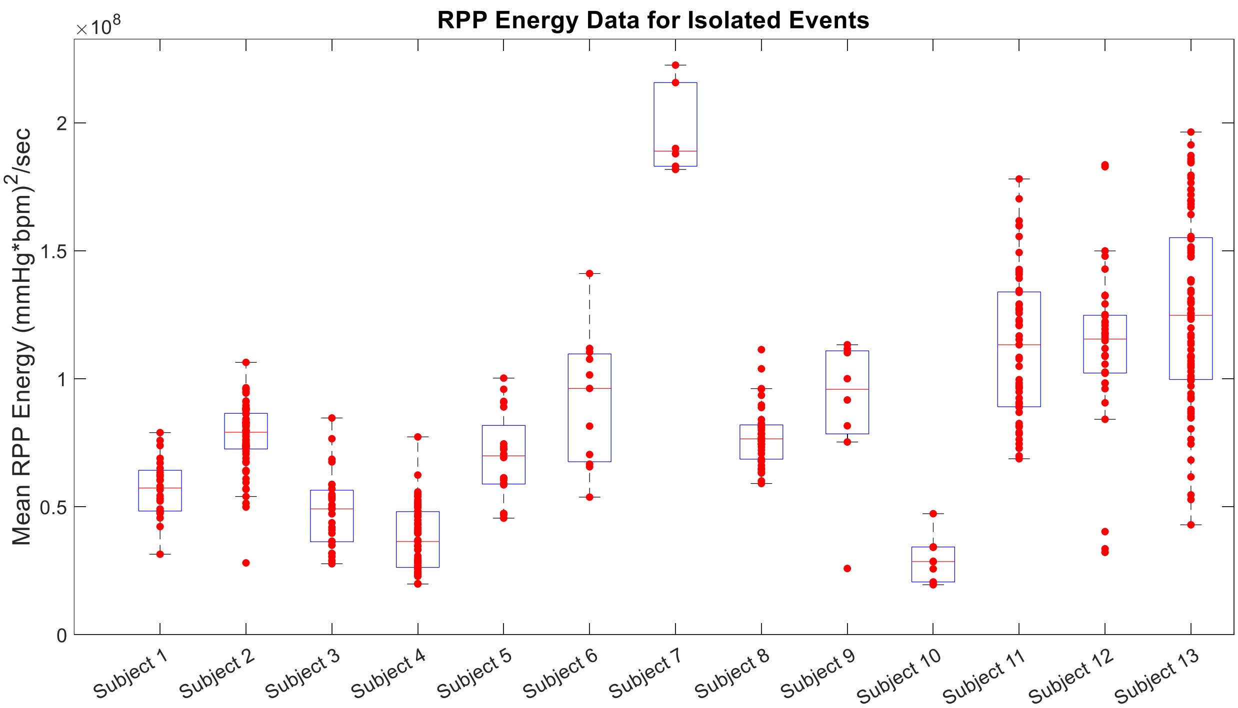

Figure 26 Box and scatterplot for normalized RPP energy during isolated events for all event types. The scatter values were used to compute column 3 of Table 9.

Table 10 Comparison of Normalized Rate Pressure Product Energy – Obstructive Sleep Apnea

Col. 1	Col. 2	Col. 3	Col. 4	Col. 5	Col. 6
Subject	**Mean REC RPP Energy $(\mathbf{mmHg} * \mathbf{bpm})^2/s$**	**Mean Isolated RPP Energy $(\mathbf{mmHg} * \mathbf{bpm})^2/s$**	**Percent Change (%)**	**Total # of Apnea RECs**	**# of Isolated Apnea Events**
1	---	---	---	0	0
2	8.22E+07	7.99E+07	-2.90	13	8
3	4.33E+07	---	---	11	0
4	4.35E+07	3.68E+07	-15.29	10	20
5	7.59E+07	7.06E+07	-7.06	47	9
6	9.41E+07	9.65E+07	2.61	15	3
7	1.83E+08	2.06E+08	12.75	50	2
8	8.72E+07	9.30E+07	6.62	5	2
9	9.49E+07	8.80E+07	-7.30	25	6
10	2.42E+07	2.69E+07	11.07	16	3
11	1.16E+08	1.56E+08	33.59	9	1
12	1.24E+08	1.30E+08	4.67	29	16
13	1.05E+08	1.15E+08	9.76	9	12
Mean ± SD	9.37E+07 ± 4.17E+07	9.98E+07 ± 5.13E+07	4.41 ± 13.09	18 ± 15	6 ± 6
T test	p = 0.17		---	---	---

Table 11 Comparison of Normalized Rate Pressure Product Energy - Hypopnea

Col. 1	Col. 2	Col. 3	Col. 4	Col. 5	Col. 6
Subject	**Mean REC RPP Energy $(\mathbf{mmHg} * \mathbf{bpm})^2/s$**	**Mean Isolated RPP Energy $(\mathbf{mmHg} * \mathbf{bpm})^2/s$**	**Percent Change (%)**	**# of Hypopnea RECs**	**# of Isolated Hypopnea Events**
1	5.89E+07	5.79E+07	-1.78	5	22
2	7.47E+07	7.69E+07	3.05	47	58
3	4.37E+07	4.91E+07	12.39	20	25
4	3.49E+07	3.83E+07	9.85	10	39
5	7.34E+07	7.05E+07	-3.94	25	10
6	8.89E+07	8.96E+07	0.79	12	8
7	1.92E+08	2.16E+08	12.19	21	1
8	7.98E+07	7.69E+07	-3.59	32	36
9	1.03E+08	9.08E+07	-11.64	14	2
10	2.68E+07	3.21E+07	19.82	8	6
11	1.08E+08	1.10E+08	1.83	49	48
12	1.13E+08	9.69E+07	-13.89	30	19
13	1.21E+08	1.29E+08	6.07	22	63
Mean ± SD	8.60E+07 ± 4.38E+07	8.72E+07 ± 4.75E+07	2.40 ± 9.69	22 ± 14	26 ± 21
T test	p = 0.66		---	---	---

3.3 Effects of Respiratory Event Chain Duration and Composition

Correlation analysis was conducted to determine if there was any linear relationship between RPP and temporal event fraction ratio (TEFR). The TEFR for RECs is defined as the ratio of time spent in a respiratory event plus 10 seconds of recovery, divided by the remainder of the time until the next event. For a detailed explanation of calculating TEFR, refer to section 2.3.3.2 in chapter 2.

Table 12 presents the results for correlation analysis between TEFR, and RPP energy/variance. Table 13 and Table 14 provide similar data, but only considering OSA and hypopnea events, respectively. The correlation coefficients as well as the p-values for a significant linear relationship are illustrated for both RPP energy and variance. The null hypothesis is that the correlation coefficient is equal to zero. The plots illustrated include three groups: all event types, only apneas, and only hypopneas.

Table 12 Correlation between rate pressure product metrics and temporal event fraction ratio for all event types

Col. 1 Subject	Col. 2 REC RPP Energy Correlation Coefficient (r)	Col. 3 REC RPP Energy Correlation p-value (p)	Col. 5 REC RPP Variance Correlation Coefficient (r)	Col. 6 REC RPP Variance Correlation p-value (p)	Col. 4 Total # of RECs
1	-0.177	0.823	-0.169	0.831	20
2	0.241	0.139	-0.137	0.406	50
3	0.135	0.550	-0.084	0.711	24
4	-0.403	0.220	0.110	0.748	16
5	-0.029	0.840	-0.207	0.145	54
6	0.192	0.511	-0.040	0.891	28
7	-0.446	0.002	0.291	0.047	51
8	-0.154	0.435	-0.362	0.058	32
9	0.200	0.316	0.014	0.945	72
10	0.143	0.584	0.672	0.003	35
11	0.192	0.186	-0.095	0.515	53
12	-0.083	0.636	-0.191	0.272	50
13	0.273	0.231	-0.048	0.838	26

Table 13 Correlation between rate pressure product metrics and temporal event fraction ratio for obstructive apnea events.

Col. 1 Subject	Col. 2 REC RPP Energy Correlation Coefficient (r)	Col. 3 REC RPP Energy Correlation p-value (p)	Col. 5 REC RPP Variance Correlation Coefficient (r)	Col. 6 REC RPP Variance Correlation p-value (p)	Col. 4 Total # of OSA RECs
1	---	---	---	---	0
2	0.502	0.310	-0.701	0.120	13
3	-0.108	0.753	0.094	0.784	11
4	0.078	0.868	0.525	0.227	10
5	-0.101	0.509	-0.143	0.348	47
6	0.192	0.511	-0.040	0.891	15
7	-0.436	0.003	0.296	0.048	50
8	-0.528	0.472	-0.376	0.624	5
9	0.097	0.660	0.241	0.281	25
10	0.270	0.313	0.649	0.007	16
11	0.329	0.472	-0.214	0.646	9
12	-0.099	0.663	0.068	0.765	29
13	0.140	0.765	-0.279	0.544	9

Table 14 Correlation between rate pressure product metrics and temporal event fraction ratio for hypopnea events.

Col. 1 Subject	Col. 2 REC RPP Energy Correlation Coefficient (r)	Col. 3 REC RPP Energy Correlation p-value (p)	Col. 5 REC RPP Variance Correlation Coefficient (r)	Col. 6 REC RPP Variance Correlation p-value (p)	Col. 4 Total # of Hypopnea RECs
1	-0.177	0.823	-0.169	0.831	5
2	0.209	0.214	-0.079	0.644	47
3	0.142	0.549	-0.075	0.754	20
4	-0.596	0.090	-0.003	0.995	10
5	-0.038	0.866	-0.297	0.179	25
6	-0.001	0.998	-0.376	0.285	12
7	-0.226	0.480	0.546	0.066	21
8	-0.154	0.435	-0.362	0.058	32
9	0.338	0.282	-0.098	0.775	14
10	-0.551	0.336	0.177	0.776	8
11	0.214	0.149	-0.091	0.545	49
12	-0.032	0.878	-0.199	0.330	30
13	0.250	0.302	-0.058	0.813	22

Across the three categories: all event types, OSA events, and hypopneas (Table 12-Table 14), there were not significant correlations between TEFR and RPP variance or energy. There were a few exceptions such as subject 7 which had significant correlations for both RPP energy and variance.

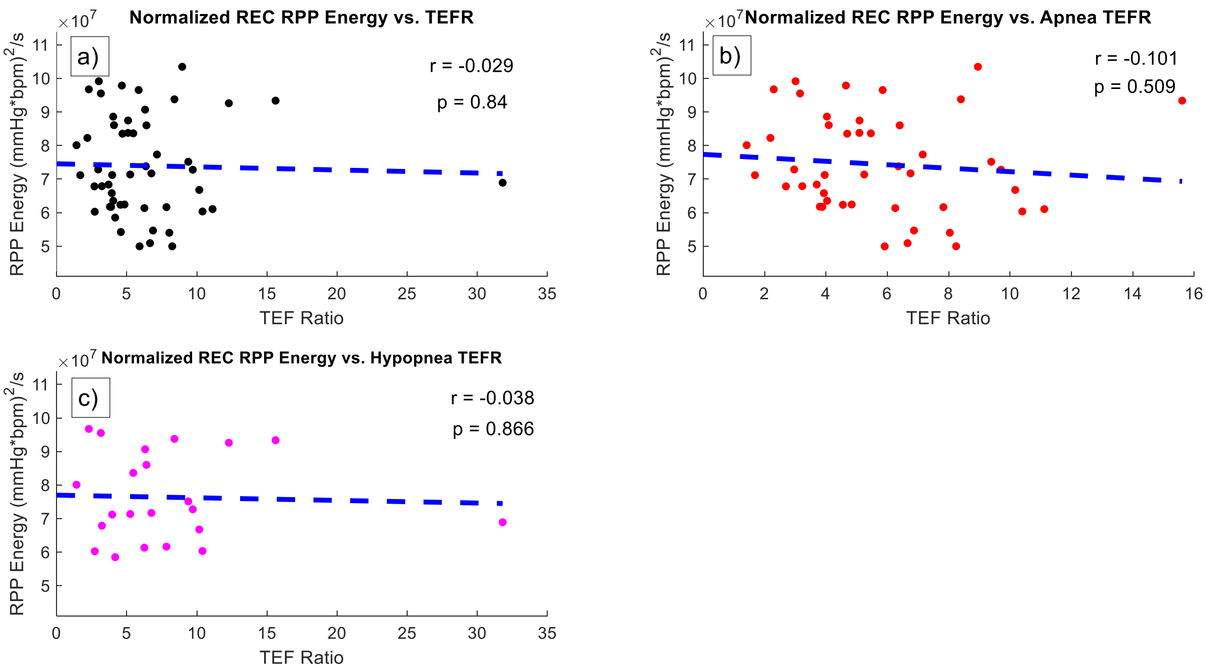

Figure 27 Correlation analysis of REC RPP energy and temporal event fraction ratio (TEFR) for subject 5. The scatterplot data in a) contains the mean respiratory event chain (REC) RPP energy for all event types. The plot in b) contains the RPP energy correlation of all RECs containing apnea events. The plot in c) contains the RPP energy correlation of all RECs containing hypopnea events. All RPP energy values are normalized with respect to event length.

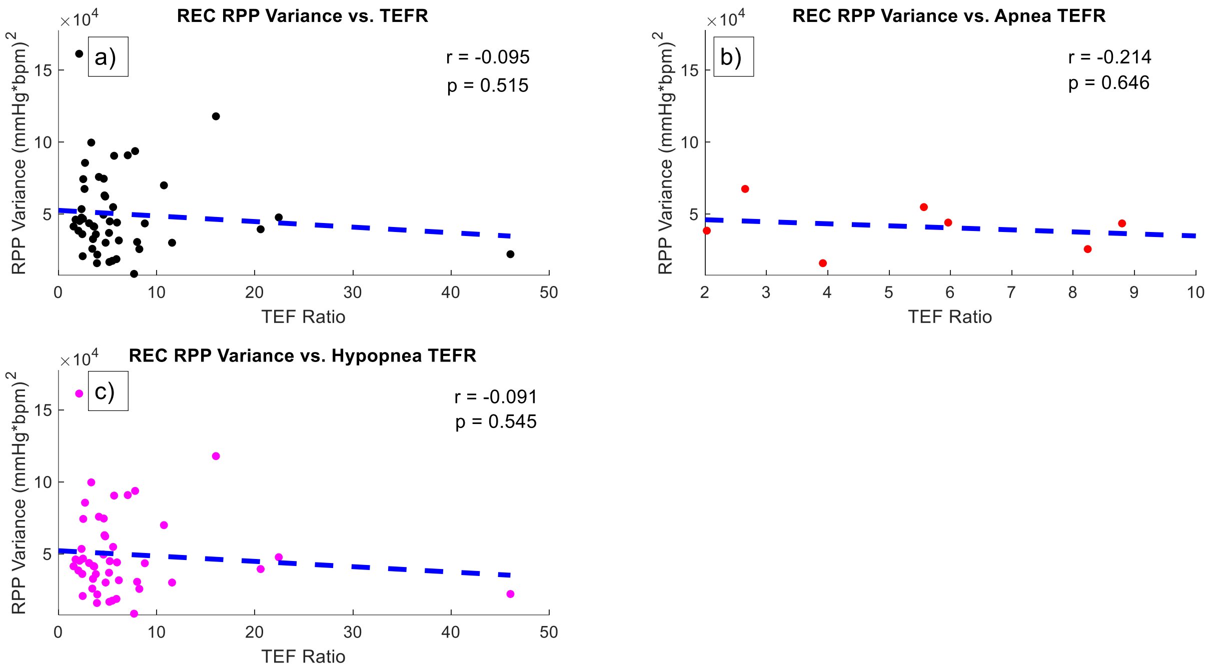

Figure 28 Correlation analysis of REC RPP variance and temporal event fraction ratio (TEFR) for subject 11. The scatterplot data in a) contains the mean respiratory event chain (REC) RPP variance for all event types. The plot in b) contains the RPP variance correlation of all RECs containing apnea events. The plot in c) contains the RPP variance correlation of all RECs containing hypopnea events. All RPP energy values are normalized with respect to event length.

A pairwise subject correlation was also conducted between the number of events occurring in RECs and the number of isolated events. There was a significant negative correlation (R = -0.67, p = 0.013) between the number of REC events and the number of isolated events as illustrated in Figure 29. The data for Figure 29 is displayed in Table 15.

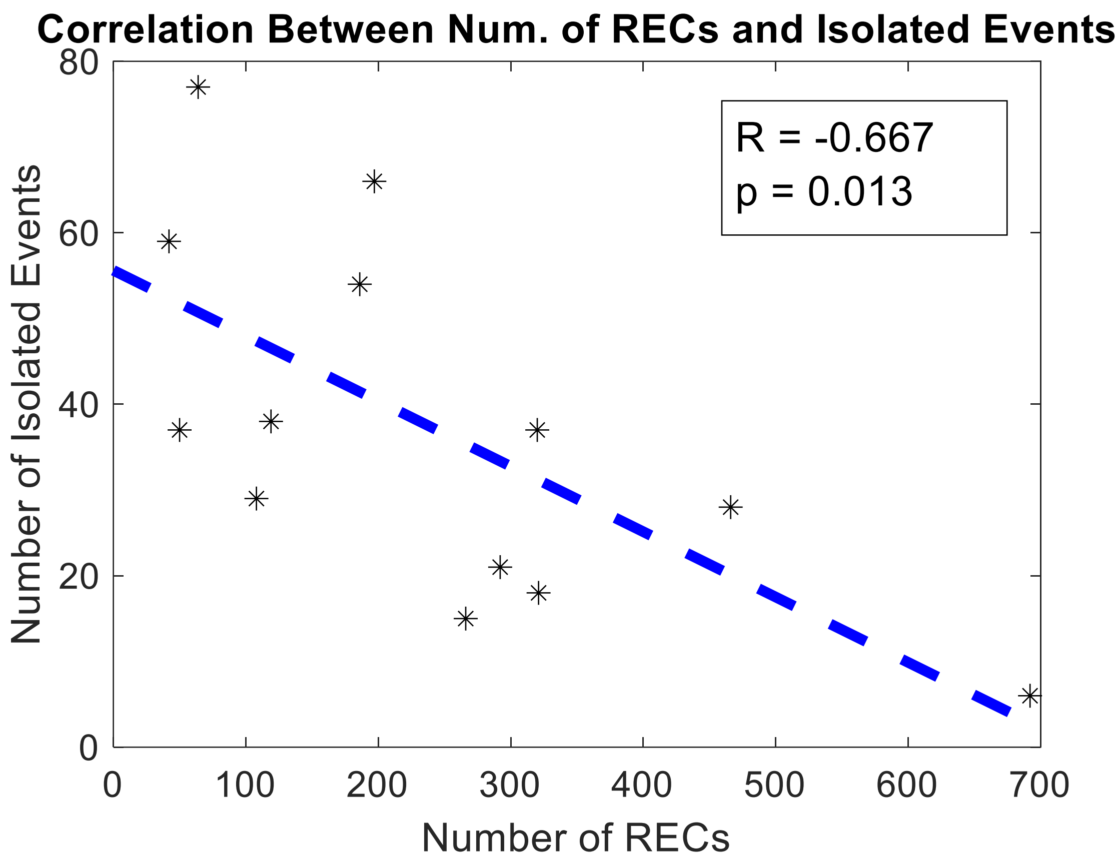

Figure 29 Correlation between number of REC events and number of isolated events for all subjects.

Table 15 Summary of number of REC events and isolated events for all subjects

Subject #	Number of REC Events	Number of Isolated Events
1	50	37
2	197	66
3	108	29
4	42	59
5	292	21
6	266	15
7	692	6
8	119	38
9	466	28
10	321	18
11	186	54
12	320	37
13	64	77

CHAPTER 4

DISCUSSION AND CONCLUSION

We aimed to investigate rate pressure product (RPP) to quantify the effects of chain respiratory events (referred to as RECs) and isolated respiratory events on cardiovascular response. Computational and statistical analyses of RPP as well as other cardiovascular metrics can contribute to understanding of the effects of respiratory events that occur in close proximity (respiratory event chains). The physiological implications of the results presented in Chapter 3 are discussed in this chapter. As well as possible future work and a comparison to current literature.

4.1. Discussion

4.1.1 Effects of Respiratory Events on Rate Pressure Product

The mean RPP analysis did not reveal any statistically significant differences between the mean RPP of respiratory event chains (RECs) and isolated events. This finding is supported both by the various statistical tests conducted on multiple event types and illustrated using the line plots. The line plot in Figure 23 reflects the small size of the difference in mean RPP, with a mix of small positive and negative differences. One interpretation is that the average cardiac work induced by a respiratory event is invariant whether the event occurs close to other events, or in isolation. Furthermore, mean RPP values did not vary significantly between baseline sleep (Table 5) and sleep with respiratory events (Table 6-Table 8). This is somewhat incongruent with results of previous studies such as Smith's group [20] which found a rise in RPP following voluntary apnea events. However, this group recorded RPP while subjects were awake, and voluntary apnea may produce different conditions than apnea during sleep. The averaging of the RPP metrics we conducted may also contribute to the differences, as the transient rise in RPP may be masked by a steady RPP waveform at the beginning of the respiratory events.

The comparison of RPP standard deviation (SD) between RECs and isolated events showed minor differences (Table 6-Table 8). The results suggest that on average REC events could have a higher RPP SD than isolated events, but the data are conflicting and inconclusive. For instance, while REC events had a higher RPP standard deviation than isolated events in 8 out of 13 subjects, there was significant variation in these metrics (Table 6). One possible interpretation is that rapidly occurring clusters of respiratory events cause a compounding effect on cardiorespiratory and nervous system feedback that results in a more volatile BP and HR. However, this compounding effect may not occur for all respiratory event types or may depend on other factors such as sleep stage. To support this interpretation: the average REC standard deviation for all subjects was higher in OSA events (Table 7) than in all event types and hypopneas alone (Table 6, Table 8).

Furthermore, none of the paired t-test p-values for differences in RPP standard deviation were statistically significant (Table 6-Table 8). As noted by Chuang [30], the return to baseline in BP following an apnea-induced BP surge is oscillatory. However, based on statistical significance from the tests conducted, the oscillations in RPP and blood pressure were not significantly different for RECs and isolated events. However, as there is considerable variation between subjects, the results are inconclusive. Examining the differences between individual subjects could explain some of the conflicting results. To elaborate, one could start by comparing the standard deviations of RPP for RECs and isolated events on a subject-by-subject basis; placing emphasis on those subjects with drastically different trends. For example, in many subjects the RPP standard deviation was higher in RECs, but looking as OSA events for subject 2, the isolated events had a much higher RPP standard deviation (Table 7).

As with the mean RPP analysis, the normalized mean RPP energy computations did not reveal significant differences between RECs and isolated events (Table 9). The analyses that considered

OSA events and hypopneas as separate categories yielded similar results (Table 10, Table 11). These results imply that on average, the cardiovascular workload per unit time does not change whether a respiratory event occurs in isolation or is quickly followed by other events.

4.1.2 Blood Pressure and Heart Rate

As RPP is a function of systolic BP (SBP) and heart rate (HR), an investigation was conducted on the individual contributions of BP and HR to the cardiovascular workload (section 3.1). The results suggest that mean SBP does not vary significantly between REC events and isolated events (Table 3). Considering that RPP is directly related to SBP, these findings are consistent with the analysis of mean RPP in section 4.1.1 (Table 6-Table 8). Standard deviation in SBP was larger in REC events than in isolated events for 10 out of 13 subjects. However, when comparing REC/isolated event standard deviation between individual subjects, the differences were relatively small (Table 3).

Similar trends were observed for HR in Table 4. The differences in mean HR between REC events and isolated events were small as illustrated by the line plot for mean HR in Figure 20. Once again, the lack of major differences in mean HR are consistent with the RPP results in section 4.1.1 (Table 6-Table 8). SBP possibly plays a larger role in variability as seen by the larger standard deviations in RPP and SBP compared to the standard deviations in HR.

4.1.3 Analysis of Respiratory Event Chain Duration and Composition

Correlation analysis was done on the relationship between the temporal event fraction ratio (TEFR) in RECs and two RPP-related metrics: RPP energy and RPP variance. For RPP energy, subjects had weak correlation coefficients in most subjects (Table 12-Table 14). Most of the correlation p-values were not significant. The correlation between RPP energy and TEFR suggests that the average cardiac work per unit time does not depend on the proportion of time spent in respiratory events.

For RPP variance, there were both positive and negative correlations across the studied categories (Table 12-Table 14). Some of these correlations were moderate ($|r| > 0.3$), but most were statistically insignificant. For OSA events, subject 10 had an abnormally large r value and was statistically significant (Table 13). The correlation results suggest that variability in cardiac workload is not significantly associated with respiratory event length.

There was a significant negative correlation between the number of RECs and isolated events when comparing all subjects (Figure 29, Table 15). Our proposed explanation is as follows: there can only be a certain number of respiratory events occurring within the sleep duration timeframe. If a larger proportion of these events occur closer together (RECs), there will be fewer isolated events in that timeframe.

4.1.4 Comparison to Current Literature

A few groups have used RPP as a surrogate for cardiac work to measure the impacts of sleep apnea on the cardiovascular system. These groups used a continuous, non-invasive method to measure blood pressure, and obtained heart rate from ECG signals. However, our study is the first to calculate instantaneous RPP using a blood pressure signal as the source for both SBP and HR. Sleep apnea has been found to consistently increase cardiac work and stress on the heart. Examples include causing increased ventricular strain and cardiovascular resistance ([15],[20]). Based on statistical significance, these findings were not supported by the results of this study. To elaborate, the baseline RPP values (Table 5), during which no apnea events occurred, were smaller than the RPP values for RECs/isolated events in most subjects (Table 6-Table 8). But when conducting a t-test, these differences were statistically insignificant. Possible factors affecting this discrepancy include: different conditions under which the studies were conducted (e.g., voluntary, simulated apnea) and the masking of transient rises in RPP by our averaging of RPP over an entire event.

Furthermore, other studies did not consider the temporal proximity of respiratory events when conducting RPP comparisons. Another novelty is our analysis of multiple event types while the other RPP sleep apnea studies focused on one apnea type (e.g., obstructive apnea, voluntary apnea while awake). The results in this preliminary study suggest that the increase in cardiac workload (RPP) induced by sleep apnea is consistent regardless of how closely or rapidly the events occur. The same applies to systolic blood pressure (SBP) and heart rate (HR).

4.1.5 Significance of Study

The comparison of respiratory events that occur in close proximity to each other with events that occur in isolation offers an important perspective for evaluating the effects of sleep apnea on the cardiovascular system. The use of instantaneous rate pressure product (IRPP) to quantify cardiac workload in closely spaced respiratory events is a novel application. In other studies, RPP has been found to follow a circadian rhythm which can be disrupted by sleep apnea [18]. The results suggest a possible increase in RPP variability during closely spaced respiratory events. Referring to previous work by Chuang [30], the peak in systolic blood pressure (SBP) which follows 5-10 seconds after an isolated event also occurred consistently in respiratory event chains (RECs). This confirms the algorithm design selection of including 10 seconds of recovery period in the analysis of SBP, HR, and RPP.

Possible future work includes the consideration of different sleep stages during the RECs. Accounting for other factors such as sleep stage, medication, gender, etc. may resolve some of the ambiguity in the RPP trends. In the context of REC composition, the type of respiratory events was not considered in the analysis. For example, in RECs the effects on RPP, BP and HR may differ for respiratory events preceded by hypopnea as opposed to those preceded by apnea. Heart rate did not vary significantly between RECs and isolated events. However, some researchers have found that obstructive sleep apnea (OSA) patients have reduced heart rate variability (HRV) compared to non-OSA patients [34]. Analyzing HRV among RECs as opposed to isolated events might yield significant results.

4.2 Conclusion

The average cardiac workload induced by sleep apnea events does not vary significantly between sleep apnea events in close proximity (< 30 seconds apart), and those in isolation (>30 seconds apart). Similar results were obtained for systolic blood pressure (SBP) and heart rate (HR). Considering the variation in RPP, there were some differences between respiratory event chains (RECs) and isolated events. However, these results were inconclusive and further investigation is required to ascertain whether the trends observed in the study are consistent. There is a need to account for other physiological factors such as sleep stages, gender and event types surrounding the RPP values. The fraction of RECs consisting of actual respiratory events, referred to as the temporal event fraction ratio (TEFR), did not have strong correlations with the RPP energy or variance.

APPENDICES

A. MATLAB CODE FOR BLOOD PRESSURE PEAK DETECTION

```
% clc; close all;clear;
rootDir = "..\\data";
%  folderNum ="1";
for q = 2:2
    folderNum = q;
global folderPath fileName;
filepath = (['C:\Users\jacku\Desktop\Sleep Apnea\converted\subject' num2str(folderNum)
'_XHz.mat'])
fileName = ([num2str(folderNum) '_XHz.mat']);
printLog('Message', sprintf('Start working on %s~~~~~~~', fileName));
m = load(filepath);
polysom = m.DataEventHypnog_Mat;
ChannelsList = m.ChannelsList;
BP_index = find(strcmp('BPWave',ChannelsList)); %M&R markers location
bp_orig = (polysom(:,BP_index))/100;
bp_mean = mean(bp_orig,'omitnan');
bp_modified = bp_orig - bp_mean;
[len,~] = size(bp_modified);
% x = 0.00: 0.0078125 :(len/128);
x = ([1:len]/128).';
% x = x(1:numel(x)-1);
%
% clear m;
%
% filepath_stg_event = (['C:\Users\jacku\Desktop\Sleep Apnea\MR_Markers\CRO_sub'
num2str(folderNum) '.mat']);
% n = load(filepath_stg_event);
```

```
%
%
%
% event = n.converted;
%
% % stage = n.STAGE;
%
% event = round(event);
% stage = round(stage);
% clear n;
%
% i = 1
% for i = 1:size(m.DAQ_rsmpl, 2)
%
% i = 4;
%
% figure;
%
% stPt = 1; endPt = 2000000;
%
% plot(x(stPt:endPt), m.DAQ_rsmpl(stPt:endPt,3));
%
%
%
% hold on;
%
% plot(x(stPt:endPt), m.DAQ_rsmpl(stPt:endPt,2));%time signal 4 synchronized
%
% plot(x(stPt:endPt), m.DAQ_rsmpl(stPt:endPt,i));
%
```

```
% plot(x(stPt:endPt), m.DAQ_rsmpl(stPt:endPt,5));
%
% plot(x(stPt:endPt), m.DAQ_rsmpl(stPt:endPt,6));
%
% plot(x(stPt:endPt), m.DAQ_rsmpl(stPt:endPt,7));
%
% plot(x(stPt:endPt), m.DAQ_rsmpl(stPt:endPt,8));
%
%
%
% plot(x(stPt:endPt),event(stPt:endPt), 'LineWidth',2, 'Color', colorConvertor('#D7BD00') );
%
% % plot(x(stPt:endPt),stage(stPt:endPt));
%
% hold off;
%
% title(sprintf('Channel: %d',i));
%
% end
%
%
%
% for find period in testing mode

targetIdx = find(x < 3340, 1, 'last');
w = 1;
getTarget = false;
% while w <= numel(wholeperiod) && getTarget == false
%
%     if targetIdx <= wholeperiod(w)
```

```
%
%         disp([w-1, wholeperiod(w-1), targetIdx]);
%
%         getTarget = true;
%
%     end
%
%     w = w + 1;
%
% end
%
%
%
%
%
% %

% Set up
global allPeakVal allPeakLc allTroughVal allTroughLc
allPeakVal = bp_modified(:) .* 0;
allPeakLc = bp_modified(:) .* 0;
allTroughVal = bp_modified(:) .* 0;
allTroughLc = bp_modified(:) .* 0;



%
% %
%
cut = floor(numel(x) * 0.015625);
```

```
wholeperiod = 1:cut:numel(x);

totalPointPeakAdd = 0;

totalPointTroughAdd = 0;

upperlimit = 1.5;

lowerlimit = 1.1;

periodIdx = 1;

% while periodIdx < 8

%  while periodIdx < 50
 while periodIdx < numel(wholeperiod)

       %disp([periodIdx,numel(wholeperiod), wholeperiod(periodIdx),wholeperiod(periodIdx
+1 )]);

   % printLog('Message',sprintf('Now Working on %d / %d  >> IDX is from %d to %d',
periodIdx,numel(wholeperiod), wholeperiod(periodIdx),wholeperiod(periodIdx +1 )));

    periodStart = wholeperiod(periodIdx);

    periodEnd = wholeperiod(periodIdx +1 );
%
%

last_bp = bp_modified(periodStart:periodEnd); %current blood pressure segment
```

```
%
printLog('Message','ALMOST DONE~~~~~~~~~~~~~~~~~~~~~~~~~~~~~');

% Finish the last part
% diff = numel(x) - wholeperiod(periodIdx);
% if diff > cut/2
% periodStart = wholeperiod(periodIdx) + cut*0.75;
% periodEnd = numel(x);
%
% else
% periodStart = wholeperiod(periodIdx);
% periodEnd = numel(x);
%
%
% end

periodStart = wholeperiod(periodIdx);
periodEnd = numel(x);

printLog('Message','ALL DONE~~~~~~~~~~~~~~~~~~~~~~~~~~~~~');

%

fig = figure('WindowState','maximized');


startPoint = 1;

plot(x(startPoint:length(x)), bp_orig(startPoint: length(bp_orig)));
```

```
hold on;

stidx = 2708651; endidx = 2708651;

plot([x(stidx) x(stidx)], [0 4], '--k');

plot([x(endidx) x(endidx)], [0 4], '--k');

%remove excessively large and small values from systolic and diastolic
%blood pressure
allPeakVal = allPeakLc + bp_mean;
allTroughVal = allTroughVal + bp_mean;

% add mean back to shift bp peaks to correct values
plot(allPeakLc, allPeakVal, 'r^');

plot(allTroughLc, allTroughVal,'v', 'Color', colorConvertor('#54009E'));
hold off;
    xlabel('Time (sec)')
    ylabel('Blood Pressure')
    title ("Peaks and Troughs - Subject " + num2str(folderNum))

%       savefig(fig,(['BP_peaksandtroughs\pk_trough_sub' num2str(folderNum) '.fig']))



[allPeakLc, allPeakVal, allTroughLc, allTroughVal] = removeZeronNan(allPeakLc,
allPeakVal, allTroughLc, allTroughVal);

%store dict variable for new data processing in "remove calibration" file
```

```
dict.peakLc = allPeakLc;
% dict.peakLc(dict.peakLc~=0);

dict.peakVal = allPeakVal;
% dict.peakVal(dict.peakVal~=0);

dict.troughLc = allTroughLc;
% dict.troughLc(dict.troughLc~=0);

dict.troughVal = allTroughVal;
% dict.troughVal(dict.troughVal~=0);

dict.x = x;
dict.y = bp_orig;

%  save((['filepath' '.mat']),'dict','-v7.3')
%  filepath_dict_old = (['filepath'.mat']);
%
%     save(filepath_dict_old, 'dict');
end
% savint2file(nan);
```

B. MATLAB CODE FOR REC DETECTION AND RPP METRICS

```
% parameters for clustering algorithm
%  epsilon_apnea = input('enter radius to search for apnea clustering neighbors (default 5e7): ')
%  epsilon_hypopnea = input('enter radius to search for hypopnea clustering neighbors (default 5e6): ')
%  minpts = input('enter minimum number of close proximity points for clustering (default 5): ')
%  %
%  ************* tables for statistical tests on RPP metrics ***********
```

```
% tables are created empty and will be filled in as each subject runs in
% the program
sz = [13 7];

%table for total number of RECs, isolated events, REC apneas, etc.
stats_totalevents_varNames = {'Subject','Total # RECs','Total # RECs w/apnea','Total # RECs w/hyp','Total # of REC events','# of REC apnea events','# of REC hyp events','Total # Isolated Events','Total # Isolated Apneas','# Isolated Hyp'};
stats_totalevents_vartypes = {'double','double','double','double','double','double','double','double','double','double'};
stats_table_totalevents = table('Size',[13 10],'VariableTypes',stats_totalevents_vartypes,'VariableNames',stats_totalevents_varNames)

%table for RPP energy metrics
stats_RPPenergy_varNames = {'Subject','Avg. Chain RPP Energy','Avg. Iso RPP Energy',...
    'Avg. Chain Apnea Energy','Avg. Iso Apnea Energy','Avg. Chain Hyp Energy','Avg. Iso Hyp Energy'};
stats_meanRPP_vartypes = {'double','double','double','double','double','double','double'};
stats_table_RPPenergy = table('Size',sz,'VariableTypes',stats_meanRPP_vartypes,...
    'VariableNames',stats_RPPenergy_varNames)

%table for RPP mean
stats_meanRPP_varNames = {'Subject','Avg. Chain RPP','Avg. Iso RPP',...
    'Avg. Chain Apnea RPP','Avg. Iso Apnea RPP','Avg. Chain Hypopnea RPP','Avg. Iso Hypopnea RPP'};
stats_table_meanRPP = table('Size',sz,'VariableTypes',stats_meanRPP_vartypes,...
    'VariableNames',stats_meanRPP_varNames)

%table for RPP standard deviation
stats_stdRPP_varNames = {'Subject','Avg. Chain RPP St. Dev.','Avg. Iso RPP St. Dev.',...
    'Avg. Chain Apnea St. Dev.','Avg. Iso Apnea St. Dev.','Avg. Chain Hyp St. Dev.','Iso Hyp St. Dev.'};
```

```
stats_table_stdRPP = table('Size',sz,'VariableTypes',stats_meanRPP_vartypes,...
    'VariableNames',stats_stdRPP_varNames)
%table for RPP variance metrics
stats_varRPP_varNames = {'Subject','Avg. Chain RPP Variance','Avg. Iso RPP Variance',...
    'Avg. Chain Apnea Variance','Avg. Iso Apnea Variance','Avg. Chain Hyp Variance','Iso Hyp Variance'};
stats_table_varRPP = table('Size',sz,'VariableTypes',stats_meanRPP_vartypes,...
    'VariableNames',stats_varRPP_varNames)
for q = 7:7
    r = 1; %counter for how many total trains have been created. regardless of their number.

    ec = 1; %counter for total number of events contained in all trains, regardless of the train
    %they occured in - per subject. used in event wise rpp calculations and plotting
sub_new = q;
filename_new = (['C:\Users\jacku\Desktop\Sleep Apnea\converted\subject' num2str(sub_new) '_XHz.mat']);
if sub_new == 11 % subject 11 was a special case with very tight calibration periods, it needed a special threshold
    filepath_cutoff = (['C:\Users\jacku\Desktop\Sleep Apnea\Chains\Rate_Pressure_Product\inst_method\correlation\calibration_cutoffs\calibration_cutoff_sub' num2str(sub_new) '.mat']);
    load(filepath_cutoff)
else
    calibration_cutoff = 1.5;
end
   % load arrays containing RECs that have missing data in order
   % to exclude them from data analysis
    filepath_missing_chains = (['C:\Users\jacku\Desktop\Sleep Apnea\Chains\Rate_Pressure_Product\inst_method\correlation\missing_chains\missing_chains_sub' num2str(sub_new) '.mat']);
    load(filepath_missing_chains)
%load figure with chains and RPP locations to visually verify the rpp correlation is
```

```
%working correctly
 filename_RPP_chains = (['C:\Users\jacku\Desktop\Sleep Apnea\Chains\Rate_Pressure_Product\inst_method\just_markers\rpp_sub' num2str(sub_new) '.fig'])
        rpp_chains_figure = openfig(filename_RPP_chains);


data_new = load(filename_new);
polysom = data_new.DataEventHypnog_Mat; %data from all polysomnography channels
ChannelsList = data_new.ChannelsList;
new_markers_index = find(strcmp('EventsResp',ChannelsList)); %M&R markers location
%extract data from polysomn using the indexes above
new_markers = polysom(:,new_markers_index); %M&R markers
bp_index = find(strcmp('BPWave',ChannelsList));
bp_orig = polysom(:,bp_index); %original blood pressure waveform
sleep_stage_index = find(strcmp('EventsAr',ChannelsList));
sleep_stage = polysom(:,sleep_stage_index);
% create time array
Time_new = ([1:length(new_markers)]/128).';
%%%%%%%%%%%%%%%%% temporary segment to plot sleep stage %%%%%%%%%%%%%%%%%%%%
% epochs_index = find(strcmp('Epochs',ChannelsList));
% epochs = polysom(:,epochs_index);
%
% figure
% yyaxis left
% plot(Time_new,bp_orig/100)
% ylim([0 4])
% ylabel('Blood Pressure','FontSize',14)
% hold on
% plot(Time_new,new_markers,'k-')
% yyaxis right
```

```
% ylabel ('Sleep Stage','FontSize',14)

% plot(Time_new,epochs,'LineWidth',2)

% ylim([0 10])

% xlabel('Time (sec)','FontSize',14)

%%%%%%%%%%%%%%%%%% end of temporary segment
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

dict_filepath = (['C:\Users\jacku\Desktop\Sleep
Apnea\Patrick_Files\dict_clean_0727\dict_clean_sub' num2str(sub_new) '.mat']);

m = load(dict_filepath);

dict = m.dict;


%%%%%%%%%%%%%%%%%% calculate RPP during "quiet" N1/N2 sleep
%%%%%%%%%%%%%%%%%%


%  current_quiet_range = find(dict.peakLc >= 1380 & dict.peakLc <= 1490);

%           quiet_range_loc = dict.peakLc(current_quiet_range); % use index to find proper range
of peak locations and values

%           quiet_range_val = dict.peakVal(current_quiet_range); % use index to find proper
range of peak locations and values

%

%

%      for f = 1:(length(quiet_range_loc)-1)

%     quiet_heartrate = quiet_range_loc(f+1) - quiet_range_loc(f);

%

%        if quiet_heartrate < calibration_cutoff % if the gap is any larger than this threshold,

%            %it's a calibration period

%           currentquiet_heartrate = (1/quiet_heartrate)*60; %heartrate at local set of peaks (bpm)

%           %currentheartrate(f) = local_heartrate; %array to store heartrate values

%

%           currentquiet_bp = quiet_range_val(f+1)*100;

%
```

```
%           quietrpp(f) = currentquiet_heartrate * currentquiet_bp; %array to store rate pressure
product
%
%           %metrics to analyze systolic blood pressure and
%           % heartrate individually. as denoted by "f" index, this
%           %computes all values for one event in a train, and then is
%           %overwritten by the next event.
%         else
%         end
%       end
%

%calculate mean and st dev of baseline (quiet sleep) RPP for current
%subject
mean_quiet_rpp = mean(nonzeros(quietrpp),'omitnan')
std_quiet_rpp = std(nonzeros(quietrpp),'omitnan')
how_many = length(current_quiet_range)
%%%%%%%%%%%%%%%%%%%% end of RPP for quiet sleep
%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%% start of pulsewidth algorithm
%%%%%%%%%%%%%%%%%%%%%%%%%%

% ****pulsewidth function needed for calculations (to tell when each event
% starts and ends).
   %temporarily convert the M&R pulses to a more basic format so that
    % pulsewidth function can calculate more accurately.

    temp_new_pulses = new_markers;
    temp_new_pulses(temp_new_pulses~=0) = 5; %convert all values that are not equal to 0 to 5
[pulse_width_mod, pulse_start_mod, pulse_end_mod] = pulsewidth(temp_new_pulses);
pulses_mod = [pulse_width_mod pulse_start_mod pulse_end_mod];
```

```
trains = zeros(length(new_markers),1);
train_loc = [];
train_value = [];

%%%%%%%%%%%%%%%%%%% end of pulsewidth algorithm
%%%%%%%%%%%%%%%%%%% %%%%%%%%%%
g = 1; %counter for columns of groups of trains
h = 1; % counter for storing event types
greater_30 = []; % stores any gaps greater than 30 seconds

  AS_index = []; %stores "weighted apnea severity" for each train.
    % the weights are as follows:
    % mixed apnea = 3
    % central apnea = 3
    % hypopnea = 2
    %obstructive apnea/apnea = 4

iso_apnea_start = ceil(pulse_start_mod);
iso_apnea_end = round(pulse_end_mod);
REC_loc = [];

% figure for plotting isolated RPP. As the program identifies isolated
%events it will aggregate them on this plot
 RPP_iso_fig = figure(6);
RPP_iso_fig.Name = "RPP Isolated Events Sub " + num2str(sub_new);
RPP_iso_fig.NumberTitle = 'off';
%RPP_iso_fig.Position = [10 100 775 675];
RPP_iso_fig.WindowState = 'Maximized';
  figure(6)
```

```
    ax1 = subplot(2,1,1); %handle to the first subplot in the figure
      plot(Time_new,new_markers*60,'k')
      xlabel('Time (sec)')
    hold on
    plot(Time_new,bp_orig)
    axis4 = gca;
    axis4.FontSize = 16;
    title("Original blood pressure subject " + num2str(sub_new) )
    xlabel('Time (sec)')
    ylabel('Blood Pressure (mmHg)')
    ylim([20 230])

 for i = 1:length(pulse_start_mod)%(length(pulse_start_mod)-1)
    % to avoid exceeding number of pulse events, add conditional for when
    % on
    %the last event in the subject.
    if i == length(pulse_start_mod) %if on the last event in the subject:
        difference = 3845; %tell the program that the difference is > 30 sec (3840 data points),
        %as we need to cut off this train and add it to the dataset.


    else
        difference = pulse_start_mod(i+1) - pulse_end_mod(i);
    end
    if  difference > 3840 % find gaps greater than 30 seconds (3840 samples)
        start = round(pulse_start_mod(h)); %start point of close event marker being examined (left
boundary of train)
        stop = round(pulse_end_mod(i)); %end point of far event marker (right boundary of train)
        if abs(h - i) >= 1 %if the strip of events includes 2 or more eventS
        trains(start:stop,g) = new_markers(start:stop);
```

```
%*** create index to exclude the trains from all events, that way only the isolated
%*** events are left. This will be used to compare the RPP of isolated
  % apneas with that of aggregated "train" apneas.
  REC_loc = [REC_loc h:i]; % this array used at the end to remove trains []
  chain = new_markers(start:stop);
  chain(:) = 2; %create base train (will be colored in later
  strip_loc = 1; %local time period of each strip

  % plot peaks during event trains 15 seconds b4 and 15 seconds after
  fifteen_before = (start - 1920); %index of 15 seconds (1920 data points) before (in seconds)
  fifteen_after = (stop + 1920);  %index of 15 seconds (1920 data points) after

   % use this set of segments to run raw blood pressure
   % in this program it is used for rate pressure product
   BP_segment = bp_orig(fifteen_before:fifteen_after);
   BP_time_segment = Time_new(fifteen_before:fifteen_after);
% plot peaks during event trains 15 seconds b4 and 15 seconds after
  fifteen_before = (start - 1920); %index of 15 seconds (1920 data points) before (in seconds)
  fifteen_after = (stop + 1920);  %index of 15 seconds (1920 data points) after

   % use this set of segments to run raw blood pressure
   % in this program it is used for rate pressure product
   BP_segment = bp_orig(fifteen_before:fifteen_after);
   BP_time_segment = Time_new(fifteen_before:fifteen_after);



  % store the duration of each train to average their duration, used
  % for metrics such as ratio of train duration/# of total
  % trains
  train_dur(g) = (stop - start) + 1280; % duration of current event train in samples
```

```
%       BP_segment = dict.peakVal(fifteen_before:fifteen_after); %*************

       BP_time_index = find(dict.peakLc*128 > fifteen_before & dict.peakLc*128 <
fifteen_after); %*****************

        pks = dict.peakVal(BP_time_index);
       locs = dict.peakLc(BP_time_index);

        % used for RPP, energy, and pie chart plots
%           first_fig = figure(1);
%           first_fig.Name = "Rate Pressure Product Subject " + num2str(sub_new);
%           first_fig.NumberTitle = 'off';
%           first_fig.WindowState = 'Maximized';

        % used for correlation between train composition and RPP energy

%           sec_fig = figure(2);
%           sec_fig.Name = "Rate Pressure Product Correlations Sub " + num2str(sub_new);
%           sec_fig.NumberTitle = 'off';
%           sec_fig.WindowState = 'Maximized';

           third_fig = figure(3);
          third_fig.Name = "Avg. Train RPP With 10 Sec Recovery Sub " + num2str(sub_new);
          third_fig.NumberTitle = 'off';
```

```
        third_fig.WindowState = 'Maximized';


        fourth_fig = figure(4);
        fourth_fig.Name = "Train RPP Variance With 10 Sec Recovery Sub " + num2str(sub_new);
        fourth_fig.NumberTitle = 'off';
        fourth_fig.WindowState = 'Maximized';


 %%%%%%%%%%%%%%%%%%%%%%%%% algorithm for calculating RPP %%%%%%%%%%%%%%%%%%%


         %%%%%%% this segment calculates RPP metrics for each train, but
      % on an  event-by-event basis


      events_per_train = abs(h-i) + 1; % since this is the difference between events, add 1 (last event counts too)



      %event_rpp_dur = [];


      for v = 1:events_per_train


        if ismember(g,missing_chains) == 0 % if the current chain is not a missing chain


        if v < events_per_train % for every event that is not the last in the train


        %after the event recorded


        event_start =  ceil(pulse_start_mod(h+v-1)); %polysom data point where the current event starts
```

```
middle_point = round(pulse_end_mod(h+v-1)); % middle point is the point where the recovery period
% (black gap) begins
event_stop = floor(pulse_start_mod(h+v)); %polysom data point where the current event stops (next event starts)



% this if statement checks how large the recovery period is. If
% it's less than 10 seconds, include entire recovery as part of
% the event. If it's more than 10 seconds, declare the event as
% only lasting 10 seconds into recovery.
recovery = (event_stop - middle_point)/128; %how long recovery period is

if recovery > 10 %10 seconds
   event_stop = middle_point + 1280; %1280 data points is 10 seconds
   t3_start = event_stop; %index used for computing revised
   %temporal event fraction (TEFr)
   t3_end = ceil(pulse_start_mod(h+v)); %notice the lack of minus 1 in (h+v)
   %the revised TEFr only applies when recovery period is
   %greater than 10 seconds
   t3_duration = t3_end - t3_start; %duration of t3 segment in samples

else %if recovery is less than 10 seconds, simply include entire recovery (that's
   % what's done by default).
   t3_duration = 0;
end



else %for the last event in the train
    event_start =  ceil(pulse_start_mod(h+v-1)); %polysom data point where the current event starts
```

```
            middle_point = round(pulse_end_mod(h+v-1)); % middle point is the point where the
recovery period
            event_stop = middle_point + 1280; %add 10 seconds to end of event

        end

    % *************visually verify that eventwise RPP is calculated correctly

        if ec <= 10
        %if ec == 115 || ec == 142 || ec == 164 || ec == 166 || ec == 200

        figure(1)
        subplot(2,1,1)
        hold on
        xline(event_start/128,'LineWidth',3,'Color','g')
        xline(middle_point/128,'LineWidth',3,'Color','b')

        xline(event_stop/128,'LineWidth',3,'Color','r')
        %xline(t3_end/128,'LineWidth',5,'Color','m')
         %xline(t3_start/128,'LineWidth',5,'Color','k')
        end

        current_rpp_dur = event_stop - event_start; %duration of current event rpp

        event_dur(ec) = current_rpp_dur; %event duration in samples (includes recovery period)
        event_fraction_all(ec) =
length(nonzeros(new_markers(event_start:event_stop)))/current_rpp_dur;
```

```
fraction_apnea_local =
(sum(new_markers(event_start:event_stop)==2))/length(new_markers(event_start:event_stop));

%fraction or percent of apnea in this event. for use in correlation between apnea
percentage in each train and

%total energy.

event_fraction_apnea(ec) = fraction_apnea_local;


fraction_hyp_local =
(sum(new_markers(event_start:event_stop)==4))/length(new_markers(event_start:event_stop));

%fraction or percent of hypopnea in this event. for use in correlation between apnea
percentage in each train and

%total energy.

event_fraction_hyp(ec) = fraction_hyp_local;


% this if statement stores duration of all events in the train

% by row, with each column being a different train.

%values will be summed by row to get total apnea duration, total hypopnea duration, etc.

% and then divided by total train duration.


if any(fraction_apnea_local) % if the value of apnea fraction is nonzero (i.e. this is an
apnea event)

    train_dur_apnea(v,g) = current_rpp_dur; % will be summed by row to get trainwise
apnea duration

    event_dur_apnea(ec) = current_rpp_dur;


     if t3_duration > 128 %(if the remaining segment of recovery is greater than 1 second

         TEFr_apnea(v,g) = current_rpp_dur/t3_duration; %ratio for apnea events in RECs

     else

     end
```

```
        elseif any(fraction_hyp_local) % if this is a hypopnea event
            train_dur_hyp(v,g) = current_rpp_dur; % will be summed by row to get train-wise hypopnea duration
            event_dur_hyp(ec) = current_rpp_dur;

            if t3_duration > 128 %(if the remaining segment of recovery is greater than 0.5 seconds
                TEFr_hyp(v,g) = current_rpp_dur/t3_duration; %ratio for hypopneas in RECs
            else
            end
        end
%           event_fraction_apnea(ec) = round(fraction_apnea_local*100,1);
%
%           event_fraction_hyp(ec) = round(fraction_hyp_local*100,1);



         %total_event_dur(ec) = current_rpp_dur/128; %used in scatter plot of total event duration vs total event energy


         train_dur_all(v,g) = current_rpp_dur; %store rpp duration (in samples) regardless of type
        if t3_duration > 128 %(if the remaining segment of recovery is greater than 1 second
         TEFr_all(v,g) = current_rpp_dur/t3_duration; %TEFr for all event
        else
        end


         current_REC_range = find(dict.peakLc >= (event_start)/128 & dict.peakLc <= (event_stop)/128);
         REC_range_loc = dict.peakLc(current_REC_range); % use index to find proper range of peak locations and values
         REC_range_val = dict.peakVal(current_REC_range); % use index to find proper range of peak locations and values
```

```
% ****************visually verify RPP is calculated correctly
if ec <= 10
%if ec == 115 || ec == 142 || ec == 164 || ec == 166 || ec == 200

    figure(1)
    subplot(2,1,1)
    plot(REC_range_loc,REC_range_val*100,'r*')
end
% calculate all RPP values for the current event in the train
currentrpp = [];
 current_bp_train = [];
 current_hr_train = [];

 for f = 1:(length(REC_range_loc)-1)
local_heartrate = REC_range_loc(f+1) - REC_range_loc(f);

    if local_heartrate < calibration_cutoff % if the gap is any larger than this threshold,
     %it's a calibration period
    currentlocal_heartrate = (1/local_heartrate)*60; %heartrate at local set of peaks (bpm)
    %currentheartrate(f) = local_heartrate; %array to store heartrate values
    currentlocal_bp = REC_range_val(f+1)*100;
    currentrpp(f) = currentlocal_heartrate * currentlocal_bp; %array to store rate pressure
product

    %metrics to analyze systolic blood pressure and
    % heartrate individually. as denoted by "f" index, this
    %computes all values for one event in a train, and then is
    %overwritten by the next event.
    current_bp_train(f) = currentlocal_bp;
    current_hr_train(f) = currentlocal_heartrate;
```

```
        else

        end

    end

    avg_bp_train(ec) = mean(nonzeros(current_bp_train),'omitnan'); % average blood pressure during each event of all trains
    avg_hr_train(ec) = mean(nonzeros(current_hr_train),'omitnan');%average heart rate during each event of all trains

    std_bp_train(ec) = std(nonzeros(current_bp_train),'omitnan'); %standard dev. of bp in each event during RECs.
    std_hr_train(ec) = std(nonzeros(current_hr_train),'omitnan');
    %the RPP energies for each event will be averaged to find
    %effects of average apnea and hypopnea in the trains

        if any(fraction_apnea_local) % if the value of apnea fraction is nonzero (i.e. this is an apnea event)
       apnea_energy_norm(v,g) = (sum(currentrpp.^2))/(current_rpp_dur/128); %will be averaged by row to get trainwise apnea energy
       elseif any(fraction_hyp_local) % if this is a hypopnea event
       hyp_energy_norm(v,g) = (sum(currentrpp.^2))/(current_rpp_dur/128); % will be averaged by row to get trainwise hyp energy

        end

    total_train_energy_norm(v,g) = (sum(currentrpp.^2))/(current_rpp_dur/128); % will be average by row to get trainwise total energy

    event_mean_rpp(ec) = mean(nonzeros(currentrpp),'omitnan'); %mean RPP of each event ocurring during a respiratory event chain.
    event_mean_rpp_norm(ec) = event_mean_rpp(ec)/(current_rpp_dur/128);
```

```
    event_std(ec) = std(nonzeros(currentrpp),'omitnan'); %standard deviation of rpp in each event occuring in trains
    event_std_norm(ec) = event_std(ec)/(current_rpp_dur/128); %normalize std with respect to event length


    event_var(ec) = var(nonzeros(currentrpp),'omitnan'); %variance of rpp each event occuring in trains
    event_var_norm(ec) = event_var(ec)/(current_rpp_dur/128); %normalized variance of rpp in each event


    %this variance is used for the revised TEF (ratio)
    event_var_TEFr(v,g) = var(nonzeros(currentrpp),'omitnan');
    event_var_TEFr_norm(v,g) = event_var_TEFr(v,g)/(current_rpp_dur/128);


    %total_event_energy_norm(v,g) = total_event_energy(ec)/total_event_dur(ec);
%
    else


        end




%
         ec = ec + 1;
%
%
%
      end
```

```
 %%%%%%%%%%%%%%%% end of algorithm for calculating RPP
%%%%%%%%%%%%%%%%%%%%%%%%

        r = r + 1;

      %else


      %end

        greater_30(i) = difference;

        event_types = new_markers(ceil(pulse_start_mod(h:i)));

        %event type of every set, ceil function to round up and make sure no zeros are accidentally
included

         g = g + 1; %counter for trains

        else %if the next apnea event 30 seconds apart is isolated (no train):

%           iso_apnea_start(ec) = start; %contains isolated apnea event start

%           iso_apnea_end(ec) = stop; %contains isolated apnea event end

%

        end

        h = i + 1; %cross the gap to the next train


    elseif isempty(greater_30) == 1 %if there are no gaps greater than 30 seconds,

        % every event in the current subject is part of one REC

        trains = new_markers;

    end

     %close all

 end  %end of train for loop
```

```
% plot correlation between train composition and RPP energy

% perform sums and averages on the values in the rows of RPP and
% event fraction arrays to get trainwise metrics.

train_dur_apnea = sum(train_dur_apnea); %train wise apnea duration
train_dur_hyp = sum(train_dur_hyp); % train-wise event duration



apnea_energy_norm(apnea_energy_norm == 0) = NaN; %replace zero with NaN

%var_apnea_energy_norm = var(apnea_energy_norm,'omitnan'); %variance of each column (all
mean_apnea_energy_norm = mean(apnea_energy_norm,'omitnan'); %compute mean of each
column (all events in a train)
apnea_trains = find(train_dur_apnea); %find trains that contained apnea
train_fraction_apnea = train_dur_apnea(apnea_trains)./train_dur(apnea_trains);
mean_apnea_energy_norm = mean_apnea_energy_norm(apnea_trains);
%var_apnea_energy_norm = var_apnea_energy_norm(apnea_trains);



hyp_energy_norm(hyp_energy_norm == 0) = NaN; %replace zero with NaN
%var_hyp_energy_norm = var(hyp_energy_norm,'omitnan');
mean_hyp_energy_norm = mean(hyp_energy_norm,'omitnan'); %compute mean of each column

hyp_trains = find(train_dur_hyp); %find trains that contained hypopnea

train_fraction_hyp = train_dur_hyp(hyp_trains)./train_dur(hyp_trains);
mean_hyp_energy_norm = mean_hyp_energy_norm(hyp_trains);
%var_hyp_energy_norm = var_hyp_energy_norm(hyp_trains);
```

```
total_train_energy_norm(total_train_energy_norm == 0) = nan;
  event_var_TEFr_norm(event_var_TEFr_norm == 0) = nan;
 %replace zero with nan so calculations are accurate
mean_train_energy_norm = mean(total_train_energy_norm,'omitnan');
 mean_TEFr_var_norm = mean(event_var_TEFr_norm,'omitnan'); %mean of variance in all
RECs. used
 %for revised TEF (TEFr)


 train_dur_all = sum(train_dur_all); %contains duration of all events in each train


 train_fraction_all = train_dur_all./train_dur;


     %compute average of revised TEF (TEFr) for each REC
        TEFr_apnea(TEFr_apnea==0) = nan;
        mean_TEFr_apnea = mean(TEFr_apnea,'omitnan');
        TEFr_apnea_index = find(~isnan(mean_TEFr_apnea)); %exclude nan values
        % a new index ("TEFr_apnea_index") was required  because a new
        % condition was imposed: events with a recovery period less than
        %10 seconds were replaced with NaN values


        TEFr_hyp(TEFr_hyp==0) = nan;
         mean_TEFr_hyp = mean(TEFr_hyp,'omitnan');
         TEFr_hyp_index = find(~isnan(mean_TEFr_hyp)); %exclude nan values


        TEFr_all(TEFr_all==0) = nan;
        mean_TEFr_all = mean(TEFr_all,'omitnan');
        TEFr_all_index = find(~isnan(mean_TEFr_all)); %exclude nan values



  figure(3)
```

```
subplot(2,2,1)
scatter(mean_TEFr_all(TEFr_all_index),mean_train_energy_norm(TEFr_all_index),...
    'ko','MarkerFaceColor','k');

 %add least squares line
 %lsline
  fig3_1 = lsline;
fig3_1.Color = 'b';
fig3_1.LineWidth = 4;
fig3_1.LineStyle = '--';

%calculate correlation coefficient
[corr_energy_train, p_energy] = corrcoef(mean_TEFr_all(TEFr_all_index).',...
    mean_train_energy_norm(TEFr_all_index).','Rows','pairwise');
corr_energy_train = corr_energy_train(1,2)
p_energy = p_energy(1,2)

% fill table with correlation coefficient (r) and p-values for linear
% relationship for all subjects
table_scatter(sub_new,1) =  corr_energy_train;
table_scatter(sub_new,2) = p_energy;

title('Normalized REC RPP Energy vs. TEF Ratio')
xlabel('TEF Ratio')
%xlim([0 100])
ylabel('RPP Energy (mmHg*bpm)^2/s')
%ylim([1e7 2.6e8])

% remove nonzero values from apnea arrays (not all events contained
% apnea, hypopnea etc.)
```

```
%    apnea_nonzero = find(event_dur_apnea); %index used to identify nonzero values
%    hyp_nonzero = find(event_dur_hyp);
    figure(3)
  subplot(2,2,2)
  scatter(mean_TEFr_all(TEFr_apnea_index),mean_train_energy_norm(TEFr_apnea_index),...
      'ro','MarkerFaceColor','r');
    %lsline
     fig3_2 = lsline;
 fig3_2.Color = 'b';
 fig3_2.LineWidth = 4;
 fig3_2.LineStyle = '--';

  [corr_apnea_energy_train, p_energy_apnea] = corrcoef(mean_TEFr_all(TEFr_apnea_index).',...
      mean_train_energy_norm(TEFr_apnea_index).','Rows','pairwise');
  corr_apnea_energy_train = corr_apnea_energy_train(1,2)
  p_energy_apnea = p_energy_apnea(1,2)

    % fill table with correlation coefficient (r) and p-values for linear
  % relationship for all subjects
  table_scatter(sub_new,3) =  corr_apnea_energy_train;
  table_scatter(sub_new,4) = p_energy_apnea;

  title('Normalized REC RPP Energy vs. Apnea TEFR')
  xlabel('TEF Ratio')
  %xlim([0 100])
  ylabel('RPP Energy (mmHg*bpm)^2/s')
  %ylim([1e7 2.6e8])
```

```
 figure(3)
 subplot(2,2,3)
 scatter(mean_TEFr_all(TEFr_hyp_index),mean_train_energy_norm(TEFr_hyp_index),...
     'mo','MarkerFaceColor','m');

  %lsline
    fig3_3 = lsline;
 fig3_3.Color = 'b';
 fig3_3.LineWidth = 4;
 fig3_3.LineStyle = '--';

 [corr_hyp_energy_train, p_energy_hyp] =
corrcoef(mean_TEFr_all(TEFr_hyp_index).',mean_train_energy_norm(TEFr_hyp_index).','Row
s','pairwise');
 corr_hyp_energy_train = corr_hyp_energy_train(1,2)
 p_energy_hyp = p_energy_hyp(1,2)

    % fill table with correlation coefficient (r) and p-values for linear
 % relationship for all subjects
 table_scatter(sub_new,5) =  corr_hyp_energy_train;
 table_scatter(sub_new,6) = p_energy_hyp;

   title('Normalized REC RPP Energy vs. Hypopnea TEFR')
 xlabel('TEF Ratio')
 %xlim([0 100])
 ylabel('RPP Energy (mmHg*bpm)^2/s')
 %ylim([1e7 2.6e8])

   filepath_corr_RPP_trains = (['C:\Users\jacku\Desktop\Sleep
Apnea\Chains\Rate_Pressure_Product\inst_method\correlation\event_by_event\recovery_10sec\t
rainwise\TEFr_ratio\rpp_energy\RPP_corr_TEFr_sub' num2str(sub_new) '.fig']);
```

```
  figure(3)
%      savefig(filepath_corr_RPP_trains);
%


% remove chain events with extreme outlier values and volatile blood
%pressure data

  if sub_new == 10
      event_var([166,168]) = nan; %variance of each event occuring in trains
      event_var_norm([166,168]) = nan;

      event_std([166,168]) = nan; %standard deviation of rpp in each event occuring in trains
      event_std_norm([166,168]) = nan;

      std_bp_train([166,168]) = nan; %standard devaition of bp in events occuring in trains
      avg_bp_train([166,168]) = nan;

      std_hr_train([166,168]) = nan;
      avg_hr_train([166,168]) = nan;




  elseif sub_new == 11
      event_var(32) = nan; %variance of each event occuring in trains
      event_var_norm(32) = nan;
```

```
    event_std(32) = nan; %standard deviation of rpp in each event occuring in trains
    event_std_norm(32) = nan;

    std_bp_train(32) = nan; %standard devaition of bp in events occuring in trains
    avg_bp_train(32) = nan;

    std_hr_train(32) = nan;
    avg_hr_train(32) = nan;

end

 % ********remove zero values *************

 event_mean_rpp(event_mean_rpp==0) = nan;
 event_mean_rpp_norm(event_mean_rpp_norm==0) = nan;

 event_std(event_std==0) = nan;
 event_std_norm(event_std_norm==0) =  nan;

 event_var(event_var==0) = nan;
 event_var_norm(event_var_norm==0) = nan;
```

```
figure(4)
subplot(2,2,1)
scatter(mean_TEFr_all(TEFr_all_index),
mean_TEFr_var_norm(TEFr_all_index),'ko','MarkerFaceColor','k');

%lsline
fig4_1 = lsline;
fig4_1.Color = 'b';
fig4_1.LineWidth = 4;
fig4_1.LineStyle = '--';

[corr_var_train, p_var] = corrcoef(mean_TEFr_all(TEFr_all_index).',...
    mean_TEFr_var_norm(TEFr_all_index).','Rows','pairwise');
corr_var_train = corr_var_train(1,2)
p_var = p_var(1,2)



% fill table with correlation coefficient (r) and p-values for linear
% relationship for all subjects
table_scatter(sub_new,7) =  corr_var_train;
table_scatter(sub_new,8) = p_var;

title('REC RPP Variance vs. TEF Ratio')
xlabel('TEF Ratio')
%xlim([0 100])
ylabel('RPP Variance (mmHg*bpm)^2')
%ylim([0 2e5])
```

```
train_apnea_nonzero = find(event_fraction_apnea);
  figure(4)
subplot(2,2,2)
scatter(mean_TEFr_all(TEFr_apnea_index),mean_TEFr_var_norm(TEFr_apnea_index),...
'ro','MarkerFaceColor','r');

  %lsline
  fig4_2 = lsline;
fig4_2.Color = 'b';
fig4_2.LineWidth = 4;
fig4_2.LineStyle = '--';


[corr_apnea_var_train, p_var_apnea] = corrcoef(mean_TEFr_all(TEFr_apnea_index).',...
   mean_TEFr_var_norm(TEFr_apnea_index).','Rows','pairwise');

corr_apnea_var_train = corr_apnea_var_train(1,2)
p_var_apnea = p_var_apnea(1,2)

    % fill table with correlation coefficient (r) and p-values for linear
% relationship for all subjects
table_scatter(sub_new,9) =  corr_apnea_var_train;
table_scatter(sub_new,10) = p_var_apnea;


title('REC RPP Variance vs. Apnea TEFR')
xlabel('TEF Ratio')
%xlim([0 100])
```

```
 ylabel('RPP Variance (mmHg*bpm)^2')
%ylim([0 2e5])


 train_hyp_nonzero = find(event_fraction_hyp);
     figure(4)
 subplot(2,2,3)

scatter(mean_TEFr_all(TEFr_hyp_index),mean_TEFr_var_norm(TEFr_hyp_index),'mo','Marker
FaceColor','m');

 %lsline

  fig4_3 = lsline;
fig4_3.Color = 'b';
fig4_3.LineWidth = 4;
fig4_3.LineStyle = '--';


 [corr_hyp_var_train, p_var_hyp] = corrcoef(mean_TEFr_all(TEFr_hyp_index).',...
     mean_TEFr_var_norm(TEFr_hyp_index).','Rows','pairwise');

 corr_hyp_var_train = corr_hyp_var_train(1,2)
 p_var_hyp = p_var_hyp(1,2)

 % fill table with correlation coefficient (r) and p-values for linear
 % relationship for all subjects
 table_scatter(sub_new,11) =  corr_hyp_var_train;
 table_scatter(sub_new,12) = p_var_hyp;
```

```
  title('REC RPP Variance vs. Hypopnea TEFR')
  xlabel('TEF Ratio')
  %xlim([0 100])
  ylabel('RPP Variance (mmHg*bpm)^2')
  %ylim([0 2e5])

   filepath_corr_RPP_var_trains = (['C:\Users\jacku\Desktop\Sleep Apnea\Chains\Rate_Pressure_Product\inst_method\correlation\event_by_event\recovery_10sec\trainwise\TEFr_ratio\rpp_variance\RPP_TEFr_var_trains_sub' num2str(sub_new) '.fig'])


   figure(4)
   %savefig(filepath_corr_RPP_var_trains);


%   *****************  % clustering algorithms **************
%     fourth_fig = figure(4);
%     fourth_fig.Name = "Clustering Algorithms Subject " + num2str(sub_new);
%             fourth_fig.NumberTitle = 'off';
%             fourth_fig.WindowState = 'Maximized';
%
%
% figure(4)
% subplot(2,2,2)
% cluster_data_apnea = [event_fraction_apnea(apnea_nonzero).' total_event_energy_norm(apnea_nonzero).'];
% idx_apnea = dbscan(cluster_data_apnea,epsilon_apnea,minpts);
```

```
%
gscatter(event_fraction_apnea(apnea_nonzero),total_event_energy_norm(apnea_nonzero),idx_ap
nea);
%   title('Apnea Clustering')
%   xlabel('Apnea %')
%   xlim([0 100])
%   ylabel('RPP Energy')
% %   %ylim([0 5e8])
%
%
%   figure(4)
% subplot(2,2,3)
% cluster_data_hyp = [event_fraction_hyp(hyp_nonzero).'
total_event_energy_norm(hyp_nonzero).'];
% idx_hyp = dbscan(cluster_data_hyp,epsilon_hypopnea,minpts);
%
gscatter(event_fraction_hyp(hyp_nonzero),total_event_energy_norm(hyp_nonzero),idx_hyp);
%   title('Hypopnea Clustering')
%   xlabel('Hypopnea %')
%   xlim([0 100])
%   ylabel('RPP Energy')
% %   %ylim([0 2.5e8])
%
%


  % **************** end of clustering ******************
%


   %close all


  % find(outliers_total_energy)
```

```
 % ****** calculate and plot RPP for isolated apnea events *************

   iso_apnea_start(REC_loc) = []; %remove train events so only isolated respiratory events are
left

   iso_apnea_end(REC_loc) = []; %remove train events so only isolated respiratory events are left



   for gg = 1:length(iso_apnea_start) % for every isolated event

       iso_RPP_start = iso_apnea_start(gg); %start point for RPP of current isolated event

       iso_RPP_middle = iso_apnea_end(gg); % middle point (end of event)

       iso_RPP_stop = iso_apnea_end(gg) + 1280; %end point



         iso_rpp_dur = iso_RPP_stop - iso_RPP_start; %duration of current event rpp

         iso_event_fraction(gg) = (iso_RPP_middle - iso_RPP_start)/iso_rpp_dur; %fraction or
percent of event

         %that was not spent in 10 seconds of recovery


            fraction_apnea_iso =
(sum(new_markers(iso_RPP_start:iso_RPP_stop)==2))/length(new_markers(iso_RPP_start:iso_
RPP_stop));

            %for use in correlation between apnea percentage in each train and

            %total energy.

            iso_fraction_apnea(gg) = round(fraction_apnea_iso*100,1);



             fraction_hyp_iso =
(sum(new_markers(iso_RPP_start:iso_RPP_stop)==4))/length(new_markers(iso_RPP_start:iso_
RPP_stop));

            %for use in correlation between apnea percentage in each train and
```

```
%total energy.
iso_fraction_hyp(gg) = round(fraction_hyp_iso*100,1);


 iso_event_dur(gg) = iso_rpp_dur/128;



    iso_range = find(dict.peakLc >= (iso_RPP_start)/128 & dict.peakLc <=
(iso_RPP_stop)/128);
        iso_range_loc = dict.peakLc(iso_range); % use index to find proper range of peak
locations and values
        iso_range_val = dict.peakVal(iso_range); % use index to find proper range of peak
locations and values



      % calculate all RPP values for the current event in the train
        iso_rpp = [];


        current_bp_iso = [];
        current_hr_iso = [];


         for a = 1:(length(iso_range_loc)-1) % for every bp value in the current isolated event
        iso_heartrate = iso_range_loc(a+1) - iso_range_loc(a);


            if iso_heartrate < calibration_cutoff
                % if the gap is any larger than threshold, it's a calibration
              isolocal_heartrate = (1/iso_heartrate)*60;
              %heartrate at local set of peaks (bpm)



             isolocal_bp = iso_range_val(a+1)*100;
```

```
            iso_rpp(a) = isolocal_heartrate * isolocal_bp;
            %array to store rate pressure product


            current_bp_iso(a) = isolocal_bp;
            current_hr_iso(a) = isolocal_heartrate;
          else
             iso_rpp(a) = nan;
          end
        end



        % ******* bp and hr metrics for isolated events ********
        if ~isempty(current_bp_iso)
        avg_bp_iso(gg) = mean(nonzeros(current_bp_iso),'omitnan'); % store avg bp during
current isolated event
        std_bp_iso(gg) = std(nonzeros(current_bp_iso),'omitnan'); % store stand. dev. of bp
during isolated events


        avg_hr_iso(gg) = mean(nonzeros(current_hr_iso),'omitnan'); % store avg hr during
current isolated event
        std_hr_iso(gg) = std(nonzeros(current_hr_iso),'omitnan');
        end




        total_iso_mean_rpp(gg) = mean(nonzeros(iso_rpp),'omitnan'); %average RPP during
each isolated event.
        total_iso_mean_rpp_norm(gg) = total_iso_mean_rpp(gg)/iso_event_dur(gg);


        total_iso_std(gg) = std(nonzeros(iso_rpp),'omitnan'); %standard devaition of RPP
during each isolated event.
        total_iso_std_norm(gg) = total_iso_std(gg)/iso_event_dur(gg);
```

```
        total_iso_var(gg) = var(nonzeros(iso_rpp),'omitnan'); %variance of all rpp values in each isolated event.
        total_iso_var_norm(gg) = total_iso_var(gg)/iso_event_dur(gg);  % variance normalized with respect to event length


        total_iso_energy(gg) = sum(iso_rpp.^2,'omitnan');
        total_iso_energy_norm(gg) = total_iso_energy(gg)/iso_event_dur(gg); % energy normalized with respect to event length



%            figure(6)
%            hold on
%            subplot(2,1,1)
%            text(Time_new(iso_RPP_start),210,"I. Event " + num2str(gg))
%
%

  %plot isolated event RPP

%    figure(6);
%    hold on
%    subplot(2,1,1);
%
plot(Time_new(iso_apnea_start(gg):iso_apnea_end(gg)),ones(length(iso_apnea_start(gg):iso_apnea_end(gg)),1).*200,'k','LineWidth',8)
%    plot(iso_range_loc,iso_range_val*100,'r*')
%

%    ax2 = subplot(2,1,2); %handle to the 2nd subplot in the figure
%     hold on
```

```
%       if isempty(iso_range_loc) == 0 % if the rpp array is not empty
%         plot(iso_range_loc,[nan iso_rpp],'r','LineWidth',1);
%         axis5 = gca;
%         axis5.FontSize = 16;
%         title("Isolated RPP subject " + num2str(sub_new))
%         xlabel('Time (sec)')
%         ylabel('RPP (mmHg*bpm)')
%
%
%     linkaxes([ax1,ax2],'x');

%       end
%



  end % end of isolated apnea events for loop





  % *********plot correlation between isolated events and RPP energy *****




  % remove extreme outliers where blood pressure data was volatile. For
  % docuemntation/reasoning, see notes

  if sub_new == 3

      total_iso_mean_rpp(23) = nan;
```

```
total_iso_mean_rpp_norm(23) = nan;

total_iso_std(23) = nan;
total_iso_std_norm(23) = nan;

 total_iso_energy(23) = NaN;
 total_iso_energy_norm(23) = NaN;

 total_iso_var(23) = nan;
 total_iso_var_norm(23) = nan;

 avg_hr_iso(23) = nan;
 std_hr_iso(23) = nan;

 avg_bp_iso(23) = nan;
 std_bp_iso(23) = nan;



elseif sub_new == 9

  total_iso_mean_rpp([8,11]) = nan;
  total_iso_mean_rpp_norm([8 11]) = nan;

  total_iso_std([8,11]) = nan;
  total_iso_std_norm([8,11]) = nan;

  total_iso_energy([8,11]) = NaN;
  total_iso_energy_norm([8,11]) = NaN;
```

```
    total_iso_var([8,11]) = nan;
    total_iso_var_norm([8,11]) = nan;

    avg_hr_iso([8,11]) = nan;
    std_hr_iso([8,11]) = nan;

    avg_bp_iso([8,11]) = nan;
    std_bp_iso([8,11]) = nan;


  elseif sub_new == 10

    total_iso_mean_rpp([4,8]) = nan;
    total_iso_mean_rpp_norm([4,8]) = nan;

    total_iso_std([4,8]) = nan;
    total_iso_std_norm([4,8]) = nan;

    total_iso_energy([4,8]) = NaN;
    total_iso_energy_norm([4,8]) = NaN;

    total_iso_var([4,8]) = nan;
    total_iso_var_norm([4,8]) = nan;

    avg_hr_iso([4,8]) = nan;
    std_hr_iso([4,8]) = nan;

    avg_bp_iso([4,8]) = nan;
    std_bp_iso([4,8]) = nan;
end
```

```
% remove zero values from isolated events (for plotting purposes)

      total_iso_mean_rpp(total_iso_mean_rpp==0) = nan;
      total_iso_mean_rpp_norm(total_iso_mean_rpp_norm==0) = nan;

      total_iso_std(total_iso_std==0) = nan;
      total_iso_std_norm(total_iso_std_norm==0) = nan;

     total_iso_energy(total_iso_energy==0) = NaN; %remove RPP where no blood pressure data
is present
     total_iso_energy_norm(total_iso_energy_norm==0) = NaN;

     total_iso_var(total_iso_var==0) = nan;
     total_iso_var_norm(total_iso_var_norm==0) = nan;


 %var_total_iso_energy = var(total_iso_energy_norm,'omitnan');


  RPP_isolated = figure(7);
 RPP_isolated.Name = "Isolated Event RPP Energy Sub " + num2str(sub_new);
 RPP_isolated.NumberTitle = 'off';
 RPP_isolated.WindowState = 'Maximized';


subplot(2,2,1)
```

```
scatter(iso_event_fraction*100,total_iso_energy_norm,'ko','MarkerFaceColor','k');
title('Normalized RPP Energy vs. Isolated Event %')
xlabel('Isolated Event %')
ylabel('Normalized RPP Energy')
xlim([0 100])
ylim([1e7 2.6e8])



  % identify whether isolated events were apnea or hypopnea
 iso_apnea_nonzero = find(iso_fraction_apnea); %index used to identify nonzero values
 iso_hyp_nonzero = find(iso_fraction_hyp);

%    var_iso_energy_apnea = var(total_iso_energy_norm(iso_apnea_nonzero),'omitnan');
%    var_iso_energy_hyp = var(total_iso_energy_norm(iso_hyp_nonzero),'omitnan');



  figure(7)
subplot(2,2,2)
scatter(iso_fraction_apnea(iso_apnea_nonzero),total_iso_energy_norm(iso_apnea_nonzero),...
'ro','MarkerFaceColor','r');
title('Isolated Apnea RPP Energy vs. Raw Apnea Percentage')
xlabel('Isolated Apnea %')
xlim([0 100])
ylabel('RPP Energy')
ylim([1e7 2.6e8])
```

```
  subplot(2,2,3)
  scatter(iso_fraction_hyp(iso_hyp_nonzero),total_iso_energy_norm(iso_hyp_nonzero),...
  'mo','MarkerFaceColor','m');

  title('Isolated Hypopnea RPP Energy vs. Raw Hypopnea Percentage')
  xlabel('Isolated Hypopnea %')
  xlim([0 100])
  ylabel('RPP Energy')
  ylim([1e7 2.6e8])



  filepath_corr_RPP_iso = (['C:\Users\jacku\Desktop\Sleep
Apnea\Chains\Rate_Pressure_Product\inst_method\correlation\event_by_event\recovery_10sec\t
rainwise\divide_by_raw_percent\rpp_avg\isolated_events\RPP_corr_isolated_sub'
num2str(sub_new) '.fig']);


   figure(7)
%  savefig(filepath_corr_RPP_iso);



RPP_isolated_var = figure(8);
   RPP_isolated_var.Name = "Isolated Event RPP Variance Sub " + num2str(sub_new);
   RPP_isolated_var.NumberTitle = 'off';
   RPP_isolated_var.WindowState = 'Maximized';


  subplot(2,2,1)
  scatter(iso_event_fraction*100, total_iso_var,'ko','MarkerFaceColor','k');
```

```
  title('Isolated RPP Variance')
  xlabel('Event %')
  xlim([0 100])
  ylabel('RPP Variance')
%ylim([0 4e5])
%
%
%
  figure(8)
    subplot(2,2,2)
   scatter(iso_fraction_apnea(iso_apnea_nonzero),total_iso_var(iso_apnea_nonzero),...
   'ro','MarkerFaceColor','r');
  title('Isolated Apnea RPP Variance')
  xlabel('Apnea %')
  xlim([0 100])
  ylabel('RPP Variance')
 %ylim([0 4e5])

%
    figure(8)
    subplot(2,2,3)
   scatter(iso_fraction_hyp(iso_hyp_nonzero),total_iso_var(iso_hyp_nonzero),...
   'mo','MarkerFaceColor','m');
  title('Isolated Hypopnea RPP Variance')
  xlabel('Hypopnea %')
  xlim([0 100])
  ylabel('RPP Variance')
  %ylim([0 4e5])
```

```
  filepath_corr_RPP_var_iso = (['C:\Users\jacku\Desktop\Sleep Apnea\Chains\Rate_Pressure_Product\inst_method\correlation\event_by_event\recovery_10sec\trainwise\divide_by_raw_percent\rpp_var\variance_of_rpp\isolated_events\RPP_corr_var_isolated_sub' num2str(sub_new) '.fig']);

  figure(8)

   %savefig(filepath_corr_RPP_var_iso);


%%%%%%%% modify y axis limits for plots %%%%%%%%%


% upper y limit for rpp variance plots

upper_RPP_var = max(max(event_var),max(total_iso_var));

upper_RPP_var = upper_RPP_var + 0.1*upper_RPP_var;


%these limits are exclusively for RPP variance in TEFr ratios

upper_var_TEFR = max(mean_TEFr_var_norm);

upper_var_TEFR = upper_var_TEFR + 0.1*upper_var_TEFR;




% lower y limit for rpp variance plots

lower_RPP_var = min(min(event_var),min(total_iso_var));

lower_RPP_var = lower_RPP_var - 0.1*lower_RPP_var;


if lower_RPP_var < 0

    lower_RPP_var = 0;

end



%these limits are exclusively for RPP variance in TEFr ratios

lower_var_TEFR = min(mean_TEFr_var_norm);

lower_var_TEFR = lower_var_TEFR - 0.1*lower_var_TEFR;
```

```
if lower_var_TEFR < 0
    lower_var_TEFR = 0;
end




% repeat for RPP energy

% upper y limit for rpp energy
upper_RPP_energy = max(max(mean_train_energy_norm),max(total_iso_energy_norm));
upper_RPP_energy = upper_RPP_energy + 0.1*upper_RPP_energy;

% lower y limit for rpp energy
lower_RPP_energy = min(min(mean_train_energy_norm),min(total_iso_energy_norm));
lower_RPP_energy = lower_RPP_energy - 0.1*lower_RPP_energy;

if lower_RPP_energy < 0
    lower_RPP_energy = 0;
end

   figure(3) % rearrange limits for RPP energy in RECs
  subplot(2,2,1)
  ylim([lower_RPP_energy upper_RPP_energy])
     text(0.9*max(mean_TEFr_all),0.90*upper_RPP_energy,"r = " +
num2str(round(corr_energy_train,3)),'FontSize',14)
     %add correlation coefficient
   text(0.9*max(mean_TEFr_all),0.80*upper_RPP_energy,"p = " +
num2str(round(p_energy,3)),'FontSize',14)
```

```
  %add correlation coefficient


  subplot(2,2,2)
 ylim([lower_RPP_energy upper_RPP_energy])
  text(0.9*max(mean_TEFr_all(TEFr_apnea_index)),0.90*upper_RPP_energy,"r = " +
num2str(round(corr_apnea_energy_train,3)),'FontSize',14)
  %add correlation coefficient
  text(0.9*max(mean_TEFr_all(TEFr_apnea_index)),0.80*upper_RPP_energy,"p = " +
num2str(round(p_energy_apnea,3)),'FontSize',14)
  %add correlation coefficient


   subplot(2,2,3)
 ylim([lower_RPP_energy upper_RPP_energy])
  text(0.9*max(mean_TEFr_all(TEFr_hyp_index)),0.90*upper_RPP_energy,"r = " +
num2str(round(corr_hyp_energy_train,3)),'FontSize',14)
  %add correlation coefficient
  text(0.9*max(mean_TEFr_all(TEFr_hyp_index)),0.80*upper_RPP_energy,"p = " +
num2str(round(p_energy_hyp,3)),'FontSize',14)
  %add correlation coefficient


  savefig(filepath_corr_RPP_trains);



   figure(4) %rearrange limits for RPP variance in RECs
 subplot(2,2,1)
 ylim([lower_var_TEFR upper_var_TEFR])
 text(0.9*max(mean_TEFr_all),0.90*upper_var_TEFR,"r = " +
num2str(round(corr_var_train,3)),'FontSize',14)
 %add correlation coefficient
 text(0.9*max(mean_TEFr_all),0.80*upper_var_TEFR,"p = " +
num2str(round(p_var,3)),'FontSize',14)
 %add correlation coeffici
```

```
subplot(2,2,2)
ylim([lower_var_TEFR upper_var_TEFR])
text(0.9*max(mean_TEFr_all(TEFr_apnea_index)),0.90*upper_var_TEFR,"r = " + num2str(round(corr_apnea_var_train,3)),'FontSize',14)
%add correlation coefficient
text(0.9*max(mean_TEFr_all(TEFr_apnea_index)),0.80*upper_var_TEFR,"p = " + num2str(round(p_var_apnea,3)),'FontSize',14)
%add correlation coefficients


subplot(2,2,3)
ylim([lower_var_TEFR upper_var_TEFR])
text(0.9*max(mean_TEFr_all(TEFr_hyp_index)),0.90*upper_var_TEFR,"r = " + num2str(round(corr_hyp_var_train,3)),'FontSize',14)
%add correlation coefficient
text(0.9*max(mean_TEFr_all(TEFr_hyp_index)),0.80*upper_var_TEFR,"p = " + num2str(round(p_var_hyp,3)),'FontSize',14)
%add correlation coeffici


savefig(filepath_corr_RPP_var_trains);


figure(7) %rearrange limits for RPP energy in isolated events
subplot(2,2,1)
ylim([lower_RPP_energy upper_RPP_energy])

subplot(2,2,2)
ylim([lower_RPP_energy upper_RPP_energy])
```

```
   subplot(2,2,3)
  ylim([lower_RPP_energy upper_RPP_energy])

   %savefig(filepath_corr_RPP_iso);



     figure(8) %rerrange limits for RPP variance in isolated events
  subplot(2,2,1)
  ylim([lower_RPP_var upper_RPP_var])
   subplot(2,2,2)
  ylim([lower_RPP_var upper_RPP_var])
   subplot(2,2,3)
  ylim([lower_RPP_var upper_RPP_var])
   %savefig(filepath_corr_RPP_var_iso);





% remove zero and very low heart rate values

avg_hr_train(avg_hr_train<=30) = nan;

std_hr_train(std_hr_train==0) = nan;

avg_hr_train(avg_hr_train==0) = nan;
avg_hr_iso(avg_hr_iso==0) = nan;
std_hr_iso(std_hr_iso==0) = nan;

avg_hr_iso(avg_hr_iso<=30) = nan;
```

```
% remove zero values for blood pressure
avg_bp_train(avg_bp_train==0) = nan;
std_bp_train(std_bp_train==0) = nan; %standard dev. of bp in each event during RECs.


avg_bp_iso(avg_bp_iso==0) = nan;
std_bp_iso(std_bp_iso==0) = nan;


  % temporary code to check for outliers/missed blood pressure surges
  % due to the 10 second breach into recovery being too short.

%    max_iso_var = max(total_iso_var_norm)
%    max_trains_var = max(event_var_norm)
%
  missed_isolated = find(total_iso_var_norm < 3000)
  missed_trains = find(event_var_norm < 3000)


% create tables and charts for results section of thesis

% *********** RPP Energy ***************************

mean_RPP_energy_trains = mean(mean_train_energy_norm,'omitnan'); %average energy per
unit time for
% all trains in current subject
mean_RPP_energy_iso = mean(total_iso_energy_norm,'omitnan'); %average energy per unit
time for
```

```
% isolated events in current subject

std_RPP_energy_trains = std(mean_train_energy_norm,'omitnan');
std_RPP_energy_iso = std(total_iso_energy_norm,'omitnan');



mean_RPP_energy_trains_apnea = mean(mean_apnea_energy_norm,'omitnan');
%average of the "average" energy per unit time for all apneas
std_RPP_energy_trains_apnea = std(mean_apnea_energy_norm,'omitnan');


mean_RPP_energy_iso_apnea = mean(total_iso_energy_norm(iso_apnea_nonzero),'omitnan');
%average of the energy per unit time for isolated apneas in current subject
std_RPP_energy_iso_apnea = std(total_iso_energy_norm(iso_apnea_nonzero),'omitnan');


mean_RPP_energy_trains_hyp = mean(mean_hyp_energy_norm,'omitnan');
%average of the "average" energy per unit time for all hypopnea trains in current subject
std_RPP_energy_trains_hyp = std(mean_hyp_energy_norm,'omitnan');


mean_RPP_energy_iso_hyp = mean(total_iso_energy_norm(iso_hyp_nonzero),'omitnan');
%average of the energy per unit time for all isolated hypopneas in current subject
std_RPP_energy_iso_hyp = std(total_iso_energy_norm(iso_hyp_nonzero),'omitnan');


%place data in table
Metrics_RPP_Energy = {'Avg. Train RPP Energy';'Avg. Isolated RPP Energy';...
    'Avg. Train Apnea Energy';'Avg. Isolated Apnea Energy';'Avg. Train Hyp Energy';...
```

```
    'Avg. Isolated Hypopnea Energy'};

Mean_RPP_Energy = [mean_RPP_energy_trains; mean_RPP_energy_iso; mean_RPP_energy_trains_apnea;
    mean_RPP_energy_iso_apnea; mean_RPP_energy_trains_hyp; mean_RPP_energy_iso_hyp];

St_Dev_RPP_Energy = [std_RPP_energy_trains; std_RPP_energy_iso; std_RPP_energy_trains_apnea;
    std_RPP_energy_iso_apnea; std_RPP_energy_trains_hyp; std_RPP_energy_iso_hyp];

% **************fill in data of subject-wise table for statistical tests

%counting total number of events (will be stored in table)
n_REC = length(find(~isnan(mean_train_energy_norm)));
%total # of RECs with viable data

n_RECapnea = length(find(~isnan(mean_apnea_energy_norm)));
%total # of RECs containing OSAs with viable data

n_REChyp = length(find(~isnan(mean_hyp_energy_norm)));
%total # of RECs containing hypopneas with viable data

n_RECevents = length(find(~isnan(avg_bp_train)));
%total # of REC events with viable data

n_RECevents_apnea = length(find(~isnan(event_var_norm(train_apnea_nonzero))));
% of OSA REC events with viable data

n_RECevents_hyp = length(find(~isnan(event_var_norm(train_hyp_nonzero))));
% of hypopnea REC events with viable data
```

```
n_iso = length(find(~isnan(avg_bp_iso)))
%number of isolated events with viable data


n_iso_apnea = length(find(~isnan(total_iso_energy_norm(iso_apnea_nonzero))))
%number of isolated OSAs with viable data


n_iso_hyp = length(find(~isnan(total_iso_energy_norm(iso_hyp_nonzero))))
%number of isolated hypopneas with viable data


% for total events table
stats_table_totalevents(sub_new,:) =
{sub_new,n_REC,n_RECapnea,n_REChyp,n_RECevents,...
    n_RECevents_apnea,n_RECevents_hyp,n_iso,n_iso_apnea,n_iso_hyp};




% for mean RPP Energy table
stats_table_RPPenergy(sub_new,:) = {sub_new,Mean_RPP_Energy(1),Mean_RPP_Energy(2),...
    Mean_RPP_Energy(3),Mean_RPP_Energy(4),Mean_RPP_Energy(5),Mean_RPP_Energy(6)};


%store data for boxplot/scatterplot
REC_RPPenergy_all(1:length(mean_train_energy_norm),sub_new) = mean_train_energy_norm;
iso_RPPenergy_all(1:length(total_iso_energy_norm),sub_new) = total_iso_energy_norm;




% for mean RPP table
```

```
stats_table_meanRPP(sub_new,:) =
{sub_new,mean(event_mean_rpp,'omitnan'),mean(total_iso_mean_rpp,...

'omitnan'),mean(event_mean_rpp(train_apnea_nonzero),'omitnan'),mean(total_iso_mean_rpp(iso
_apnea_nonzero),'omitnan'),...

mean(event_mean_rpp(train_hyp_nonzero),'omitnan'),mean(total_iso_mean_rpp(iso_hyp_nonze
ro),'omitnan')};



% store data for boxplot/scatterplot

REC_meanRPP_all(1:length(event_mean_rpp),sub_new) = event_mean_rpp;

iso_meanRPP_all(1:length(total_iso_mean_rpp),sub_new) = total_iso_mean_rpp;




% for RPP standard deviation table

stats_table_stdRPP(sub_new,:) =
{sub_new,mean(event_std,'omitnan'),mean(total_iso_std,'omitnan'),...


mean(event_std(train_apnea_nonzero),'omitnan'),mean(total_iso_std(iso_apnea_nonzero),'omitn
an'),...


mean(event_std(train_hyp_nonzero),'omitnan'),mean(total_iso_std(iso_hyp_nonzero),'omitnan')}
;


% for RPP variance table

stats_table_varRPP(sub_new,:) =
{sub_new,mean(event_var,'omitnan'),mean(total_iso_var,'omitnan'),...


mean(event_var(train_apnea_nonzero),'omitnan'),mean(total_iso_var(iso_apnea_nonzero),'omitn
an'),...


mean(event_var(train_hyp_nonzero),'omitnan'),mean(total_iso_var(iso_hyp_nonzero),'omitnan')
};
```

```
% for blood pressure
REC_bp_all(1:length(avg_bp_train),sub_new) = avg_bp_train;
iso_bp_all(1:length(avg_bp_iso),sub_new) = avg_bp_iso;

% for heart rate
REC_hr_all(1:length(avg_hr_train),sub_new) = avg_hr_train;
iso_hr_all(1:length(avg_hr_iso),sub_new) = avg_hr_iso;



% when no apneas or hypopneas present, need to add conditional to fill in
% gaps of missing data in the tables



if isempty(max(mean_apnea_energy_norm)) ||
isempty(max(total_iso_energy_norm(iso_apnea_nonzero)))
    % if either no apneas in trains or no apneas in isolated events, you
    % can't compare the two, so replace with NaN
    Max_RPP_Energy = [max(mean_train_energy_norm); max(total_iso_energy_norm);
        nan; nan; max(mean_hyp_energy_norm); max(total_iso_energy_norm(iso_hyp_nonzero))];

    Min_RPP_Energy = [min(mean_train_energy_norm); min(total_iso_energy_norm);
        nan; nan; min(mean_hyp_energy_norm); min(total_iso_energy_norm(iso_hyp_nonzero))];

elseif isempty(max(mean_hyp_energy_norm)) ||
isempty(max(total_iso_energy_norm(iso_hyp_nonzero)))
        % if either no hypopneas in trains or no hypopneas in isolated events, you
    % can't compare the two, so replace with NaN
    Max_RPP_Energy = [max(mean_train_energy_norm); max(total_iso_energy_norm);
        max(mean_apnea_energy_norm); max(total_iso_energy_norm(iso_apnea_nonzero)); nan;
nan];
```

```
    Min_RPP_Energy = [min(mean_train_energy_norm); min(total_iso_energy_norm);
        min(mean_apnea_energy_norm); min(total_iso_energy_norm(iso_apnea_nonzero)); nan;
nan];

else
    % if both apneas and hypopneas present, no NaN entries needed
    Max_RPP_Energy = [max(mean_train_energy_norm); max(total_iso_energy_norm);
        max(mean_apnea_energy_norm); max(total_iso_energy_norm(iso_apnea_nonzero));
        max(mean_hyp_energy_norm); max(total_iso_energy_norm(iso_hyp_nonzero))];

    Min_RPP_Energy = [min(mean_train_energy_norm); min(total_iso_energy_norm);
        min(mean_apnea_energy_norm); min(total_iso_energy_norm(iso_apnea_nonzero));
        min(mean_hyp_energy_norm); min(total_iso_energy_norm(iso_hyp_nonzero))];

end



RPP_Results =
table(Metrics_RPP_Energy,Mean_RPP_Energy,St_Dev_RPP_Energy,Max_RPP_Energy,Min_R
PP_Energy)




 RPP_Energy_fig = figure(9);
        RPP_Energy_fig.Name = "Avg. Train RPP Energy Sub " + num2str(sub_new);
        RPP_Energy_fig.NumberTitle = 'off';
        RPP_Energy_fig.WindowState = 'Maximized';

figure(9)
```

```
bar_y = [Mean_RPP_Energy(1) Mean_RPP_Energy(2); Mean_RPP_Energy(3)...
    Mean_RPP_Energy(4); Mean_RPP_Energy(5) Mean_RPP_Energy(6)];

bar(bar_y);
title("RPP Energy of Trains and Isolated Events Sub " + num2str(sub_new),'FontSize',20)
ylabel('Mean RPP Energy','FontSize',18)
legend('Trains','Isolated Events')

hold on
set(gca,'xticklabel',{'Total RPP','Apnea RPP','Hypopnea RPP'},'FontSize',16)

 %bar([1 2 4 5 7 8],Mean)
% p1 = bar([1 4 7],Mean_RPP_Energy(1:2:5));
% %set(gca,'xticklabel',{'Train Energy','Isolated Energy'})
% hold on;
% p2 = bar([4 5],Mean_RPP_Energy(3:4));
% %set(gca,'xticklabel',{'Train Ap. Energy','Isolated Ap. Energy'})
% hold on
% p3 = bar([7 8],Mean_RPP_Energy(5:6));
% %set(gca,'xticklabel',{'Train Hyp. Energy','Isolated Hyp. Energy'})
%
% set(p1,'FaceColor','grey');
% set(p2,'FaceColor','red');
% set(p3,'FaceColor','magenta');
% set(gca,'xticklabel',{'Mean Train Energy','Isolated RPP Energy', 'Mean Train Ap. Energy',...
%'Isolated Ap. Energy', 'Train Hyp Energy', 'Isolated Hyp Energy'})
%  title("RPP Metrics for Trains and Isolated Events Sub " + num2str(sub_new),'FontSize',20)
%  ylabel('Mean','FontSize',20)
%
```

```
% create error bars
ngroups = size(bar_y,1);
nbars = size(bar_y,2);

err = [St_Dev_RPP_Energy(1) St_Dev_RPP_Energy(2); St_Dev_RPP_Energy(3)
St_Dev_RPP_Energy(4);
    St_Dev_RPP_Energy(5) St_Dev_RPP_Energy(6)];

% Calculating the width for each bar group
groupwidth = min(0.8, nbars/(nbars + 1.5));
for i = 1:nbars
    x = (1:ngroups) - groupwidth/2 + (2*i-1) * groupwidth / (2*nbars);
    errorbar(x, bar_y(:,i), err(:,i), '.','Color',[0 0 0],'LineWidth',3);
end

legend('Trains','Isolated Events','','')

mean_RPP_filepath = (['C:\Users\jacku\Desktop\Sleep
Apnea\Chains\Rate_Pressure_Product\inst_method\correlation\event_by_event\recovery_10sec\t
rainwise\thesis_results\mean_RPP_metrics_sub' num2str(sub_new) '.fig']);
savefig(mean_RPP_filepath);

% *************** end of RPP Energy ***************

bp_train_allsub(sub_new) = mean(avg_bp_train,'omitnan');
% average of all the average systolic blood pressures during each event
bp_std_train_allsub(sub_new) = mean(std_bp_train,'omitnan');
%average of all bp stand. dev. during RECs

hr_train_allsub(sub_new) = mean(avg_hr_train,'omitnan');
% average of all the average heart rate during each event.
```

```
hr_std_train_allsub(sub_new) = mean(std_hr_train,'omitnan');
%avg of all heart rate std dev. during RECs.

bp_iso_allsub(sub_new) = mean(avg_bp_iso,'omitnan');
bp_std_iso_allsub(sub_new) = mean(std_bp_iso,'omitnan');
%avg of bp stand. dev. during all isolated events

hr_iso_allsub(sub_new) = mean(avg_hr_iso,'omitnan');
hr_std_iso_allsub(sub_new) = mean(std_hr_iso,'omitnan');

% search for outliers in RPP metrics
outliers_var_iso = find(isoutlier(total_iso_var_norm))
outliers_var_chains = find(isoutlier(event_var_norm))



% this dataset used in correlation analysis between total # of RECs and
%total # of isolated events

w = length(REC_loc); %total # of RECs, regardless of
%whether they contained blood pressure data or not
ww = length(iso_apnea_start); %total # of isolated events,
%regardless of whether they contained blood pressure data or not

data_corr_nevents(sub_new,1:2) = [w ww]

%     clearvars -except bp_train_allsub  bp_std_train_allsub  hr_train_allsub  hr_std_train_allsub
bp_iso_allsub  bp_std_iso_allsub  hr_iso_allsub  hr_std_iso_allsub  stats_table_RPPenergy
stats_table_meanRPP stats_table_stdRPP stats_table_varRPP table_scatter
stats_table_totalevents REC_meanRPP_all iso_meanRPP_all REC_RPPenergy_all
iso_RPPenergy_all REC_bp_all iso_bp_all REC_hr_all iso_hr_all data_corr_nevents
%     clc
```

```
%    close all
% end of subject-wise for loop



end


% correlation calculations for total number of RECs and isolated events
 [corr_total_events, p_total_events] = corrcoef(data_corr_nevents(:,1),data_corr_nevents(:,2),...
     'Rows','pairwise');


% "before-after" plots for individual blood pressure and heart rate
%create tables for statistical analysis


stats_individual_varNames = {'Subject','REC Blood Pressure','Isolated Event Blood Pressure',...
    'REC BP Standard Deviation ','Isolated BP Standard Deviation', 'REC Heart Rate',...
    'Isolated Event HR','REC HR Standard Deviation','Isolated HR Standard Deviation'};


stats_individual_vartypes = {'double','double','double','double','double','double',...
    'double','double','double'};
stats_table_individual = table('Size',[13 9],'VariableTypes',stats_individual_vartypes,...
'VariableNames',stats_individual_varNames)


%subject comparison of average systolic blood pressure
figure
hold on
for z = 1:length(bp_train_allsub)
plot([1 2],[bp_train_allsub(z) bp_iso_allsub(z)],'k','LineWidth',2)
%text(0.8,bp_train_allsub(z),"Diff: " + num2str(bp_iso_allsub(z) - bp_train_allsub(z)) + "
mmHg")
stats_table_individual(z,:) = {z, bp_train_allsub(z), bp_iso_allsub(z),bp_std_train_allsub(z),...
```

```
    bp_std_iso_allsub(z),hr_train_allsub(z),hr_iso_allsub(z),hr_std_train_allsub(z),
hr_std_iso_allsub(z)};

end




title('Systolic BP Comparison all Subjects')

ylabel('Average Blood Pressure (mmHg)')

xlim([0.5 2.5])

xticks([1 2])

set(gca,'xticklabel',{'RECs','Isolated Events'},'FontSize',16)



% plot subject comparison of mean RPP

figure

hold on

for z = 1:length(bp_train_allsub)

plot([1 2],[stats_table_meanRPP{z,2} stats_table_meanRPP{z,3}],'k','LineWidth',2)

%text(0.8,bp_train_allsub(z),"Diff: " + num2str(bp_iso_allsub(z) - bp_train_allsub(z)) + "
mmHg")

end


title('Mean RPP Comparison all Subjects')

ylabel('Average RPP (mmHg*bpm/sec)')

xlim([0.5 2.5])

xticks([1 2])

set(gca,'xticklabel',{'RECs','Isolated Events'},'FontSize',16)
```

```
% plot subject comparison of RPP standard deviation

figure

hold on

for z = 1:length(bp_train_allsub)

plot([1 2],[stats_table_stdRPP{z,2} stats_table_stdRPP{z,3}],'k','LineWidth',2)

%text(0.8,bp_train_allsub(z),"Diff: " + num2str(bp_iso_allsub(z) - bp_train_allsub(z)) + "
mmHg")

end


title('RPP Standard Deviation all Subjects')

ylabel('RPP S.D. (mmHg*bpm/sec)')

xlim([0.5 2.5])

xticks([1 2])

set(gca,'xticklabel',{'RECs','Isolated Events'},'FontSize',16)


% plot subject comparison of heart rate

figure

hold on

for z = 1:length(hr_train_allsub)

plot([1 2],[hr_train_allsub(z) hr_iso_allsub(z)],'k','LineWidth',2)

%text(0.8,hr_train_allsub(z),"Diff: " + num2str(hr_iso_allsub(z) - hr_train_allsub(z)) + " bpm")

end


title('Heart Rate Comparison all Subjects')

ylabel('Average Heart Rate (bpm)')

xlim([0.5 2.5])

xticks([1 2])

set(gca,'xticklabel',{'RECs','Isolated Events'},'FontSize',16)
```

```
%create boxplots/scatterplots for all subjects on various metrics

REC_meanRPP_all(REC_meanRPP_all==0) = nan;
iso_meanRPP_all(iso_meanRPP_all==0) = nan;
REC_RPPenergy_all(REC_RPPenergy_all==0) = nan;
iso_RPPenergy_all(iso_RPPenergy_all==0) = nan;
REC_bp_all(REC_bp_all==0) = nan;
iso_bp_all(iso_bp_all==0) = nan;

REC_hr_all(REC_hr_all==0) = nan;
iso_hr_all(iso_hr_all==0) = nan;
figure
title('Mean RPP Data for RECs')
ylabel('Mean RPP')
hold on
boxplot(REC_meanRPP_all,'positions',[1:13],'labels',{'Subject 1','Subject 2',...
    'Subject 3','Subject 4','Subject 5','Subject 6','Subject 7','Subject 8','Subject 9',...
    'Subject 10','Subject 11','Subject 12','Subject 13'})
swarmchart([1:13],REC_meanRPP_all,'filled','red')
figure
title('Mean RPP Data for Isolated Events')
ylabel('Mean RPP')
hold on
boxplot(iso_meanRPP_all,'positions',[1:13],'labels',{'Subject 1','Subject 2','Subject 3',...
    'Subject 4','Subject 5','Subject 6','Subject 7','Subject 8','Subject 9','Subject 10',...
    'Subject 11','Subject 12','Subject 13'})
swarmchart([1:13],iso_meanRPP_all,'filled','red')
figure
title('RPP Energy Data for RECs')
```

```
ylabel('Mean RPP Energy')
hold on
boxplot(REC_RPPenergy_all,'positions',[1:13],'labels',{'Subject 1','Subject 2','Subject 3',...
    'Subject 4','Subject 5','Subject 6','Subject 7','Subject 8','Subject 9','Subject 10',...
    'Subject 11','Subject 12','Subject 13'})
swarmchart([1:13],REC_RPPenergy_all,'filled','red')
figure
title('RPP Energy Data for Isolated Events')
ylabel('Mean RPP Energy')
hold on
boxplot(iso_RPPenergy_all,'positions',[1:13],'labels',{'Subject 1','Subject 2','Subject 3',...
    'Subject 4','Subject 5','Subject 6','Subject 7','Subject 8','Subject 9','Subject 10',...
    'Subject 11','Subject 12','Subject 13'})

swarmchart([1:13],iso_RPPenergy_all,'filled','red')
figure
title('Systolic BP Data for RECs')
ylabel('Systolic BP (mmHg)')
hold on
boxplot(REC_bp_all,'positions',[1:13],'labels',{'Subject 1','Subject 2','Subject 3',...
    'Subject 4','Subject 5','Subject 6','Subject 7','Subject 8','Subject 9','Subject 10',...
    'Subject 11','Subject 12','Subject 13'})
swarmchart([1:13],REC_bp_all,'filled','red')

figure
title('Systolic BP Data for Isolated Events')
ylabel('Systolic BP (mmHg)')
hold on
boxplot(iso_bp_all,'positions',[1:13],'labels',{'Subject 1','Subject 2','Subject 3',...
    'Subject 4','Subject 5','Subject 6','Subject 7','Subject 8','Subject 9','Subject 10',...
```

```
    'Subject 11','Subject 12','Subject 13'})
swarmchart([1:13],iso_bp_all,'filled','red')

figure
title('Heart Rate Data for RECs')
ylabel('Heart Rate (bpm)')
hold on
boxplot(REC_hr_all,'positions',[1:13],'labels',{'Subject 1','Subject 2','Subject 3',...
    'Subject 4','Subject 5','Subject 6','Subject 7','Subject 8','Subject 9','Subject 10',...
    'Subject 11','Subject 12','Subject 13'})
swarmchart([1:13],REC_hr_all,'filled','red')

figure
title('Heart Rate Data for Isolated Events')
ylabel('Heart Rate (bpm)')
hold on
boxplot(iso_hr_all,'positions',[1:13],'labels',{'Subject 1','Subject 2','Subject 3',...
    'Subject 4','Subject 5','Subject 6','Subject 7','Subject 8','Subject 9','Subject 10',...
    'Subject 11','Subject 12','Subject 13'})
swarmchart([1:13],iso_hr_all,'filled','red')

% *********** output table for statistical tests on all subjects
stats_table_totalevents
stats_totalevents_filename = (['C:\Users\jacku\Desktop\Sleep
Apnea\Chains\Rate_Pressure_Product\inst_method\correlation\event_by_event\recovery_10sec\t
rainwise\thesis_results\matlab_stats_totalevents.xlsx']);
 %writetable(stats_table_totalevents,stats_totalevents_filename,'Sheet',1,'Range','A1')
```

```
stats_table_individual

 % save table as excel spreadsheet

 stats_individual_filename = (['C:\Users\jacku\Desktop\Sleep Apnea\Chains\Rate_Pressure_Product\inst_method\correlation\event_by_event\recovery_10sec\trainwise\thesis_results\matlab_stats_individual.xlsx']);

%writetable(stats_table_individual,stats_individual_filename,'Sheet',1,'Range','A1')


stats_table_RPPenergy

 % save table as excel spreadsheet

stats_RPPenergy_filename = (['C:\Users\jacku\Desktop\Sleep Apnea\Chains\Rate_Pressure_Product\inst_method\correlation\event_by_event\recovery_10sec\trainwise\thesis_results\matlab_stats_RPPenergy.xlsx']);

%writetable(stats_table_RPPenergy,stats_RPPenergy_filename,'Sheet',1,'Range','A1')


stats_table_meanRPP

stats_meanRPP_filename = (['C:\Users\jacku\Desktop\Sleep Apnea\Chains\Rate_Pressure_Product\inst_method\correlation\event_by_event\recovery_10sec\trainwise\thesis_results\matlab_stats_meanRPP.xlsx']);

%writetable(stats_table_meanRPP,stats_meanRPP_filename,'Sheet',1,'Range','A1')


stats_table_stdRPP

stats_stdRPP_filename = (['C:\Users\jacku\Desktop\Sleep Apnea\Chains\Rate_Pressure_Product\inst_method\correlation\event_by_event\recovery_10sec\trainwise\thesis_results\matlab_stats_stdRPP.xlsx']);

%writetable(stats_table_stdRPP,stats_stdRPP_filename,'Sheet',1,'Range','A1')


stats_table_varRPP

stats_varRPP_filename = (['C:\Users\jacku\Desktop\Sleep Apnea\Chains\Rate_Pressure_Product\inst_method\correlation\event_by_event\recovery_10sec\trainwise\thesis_results\matlab_stats_varRPP.xlsx']);

%writetable(stats_table_varRPP,stats_varRPP_filename,'Sheet',1,'Range','A1')

%output table with correlation coefficients and p-values

table_scatter
```

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