# Sleep Arousal and Cardiovascular Dynamics

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# Abstract

Sleep arousal conventionally refers to any temporary intrusions of wakefulness into sleep. Arousals are usually considered as a part of normal sleep and rarely result in complete awakening. However, once their frequency increases, they may affect the sleep architecture and lead to sleep fragmentation, resulting in fatigue, poor executive functioning and excessive daytime sleepiness. In the electroencephalogram, arousals mostly appear as a shift of power in frequency to values greater than 16 Hz lasting 3-15 seconds. The general objective of this thesis was to investigate on the nature of sleep arousal and study arousal interaction and association with cardiovascular dynamics.

At the first step of this research, an algorithm was developed and evaluated for automatic detection of sleep arousal. The polysomnographic (PSG) data of 9 subjects were analysed and 32 features were derived from a range of biosignals. The extracted features were used to develop kNN classifier model in to differentiate arousal from non-arousal events. The developed algorithm can detect arousal events with the average sensitivity and accuracy of 79% and 95.5%, respectively.

The second aim was to investigate cardiovascular dynamics once an arousal occurs. Overnight continuous systolic and diastolic blood pressure (SBP and DSP), spectral components of heart rate variability (HRV) and the pulse transit time of 10 subjects (average arousal number of $51.5 \pm 21.1$ per person) were analysed before and after arousal occurrence. Whether each cardiovascular variable increases or decreases was evaluated in different types of arousals through slpoe index (SI). The analysis indicated a post-arousal SBP and DBP elevation and PTT dropping. High frequency component of HRV (HF) dropped at arousal onset whilst low frequency

(LF) component shifted.

HRV spectral components extracted from ECG, lead I alongside with PTT were utilised for sleep staging in 22 healthy and insomnia subjects using linear and non-linear classifier models. Obtained result shows that developed model by DW-kNN classifier could detect sleep stages with mean accuracy of 73.4% $\pm$ 6.4.

An empirical curve fitting model for overnight continuous blood pressure estimation was developed and evaluated using the first and second derivatives of fingertip PPG (VPG, APG) along with ECG. The *VPG-based* model could estimate systolic and diastolic blood pressure with mean error of $\pm$3.96 *mmHg* with standard deviation of 1.41 *mmHg* and DBP with $\pm$6.88 *mmHg* with standard deviation of 3.03 *mmHg*.

The QT and RR time intervals are two cardiac variables which represent beat to beat variability and ventricular repolarisation, respectively. PSG dataset of 2659 men aged older than 65 (MrOS Sleep Study) was analysed to compare on RR and QT interval variability pre- and post-arousal onset. The cardiac interval gradients were developed to monitor instantaneous changes pre-and post-onset. Analysis of gradients demonstrated that both RR and QT are likely to start shortening several second prior to onset by average probability of 73% and 64%. The QT/RR linear correlation was significantly rising after arousal inducing regardless of arousal type and associated pathological events ($R_{post}$ = 0.218 vs $R_{pre}$ = 0.047). ANOVA test and Tukey's honest post-hoc analysis indicated a significant difference between cardiac intervals variability between respiratory, movements and spontaneous arousals. In addition, respiratory disturbance index (RDI) as a measure of sleep apnoea severity was reversely correlated with both QT ($R_{VarQT}$ = -0.251, $p < 0.0001$) and RR intervals vs ($R_{VarRR}$ = -0.265, $p < 0.0001$). The stronger QT and RR intervals variability in shorter arousal ($duration < 8$) than longer episodes indicates that cardiac variability is reversely associated with arousal duration ($p < 0.0001$). Sleep stage effect was significant in both cardiac interval variability, particularly in RR intervals.

Analysis of arousal related cardiac intervals variability in male participants with different medical history indicated an association between post arousal un-

changed or descending QT ($\Delta QT > 1.1$ ms) and greater frequency of sleep arousal, less physical activity and medical history of several cardiovascular disease. Similarly participants in quartile $\Delta RR > -8.8$ were likelier to be obese with less physical activity, medical history of COPD and stroke and suffered from severer degree of sleep apnoea ($RDI = 28.7 \pm 20.4$ vs $RDI = 25.5 \pm 17.6$, $p < 0.001$). Kaplan-Meier analysis showed that the distribution $\Delta RR$ at arousal onset was significantly associated with cardiovascular (CV) mortality ($p < 0.001$). Cox proportional hazard regression models also indicated the effect of arousal duration in prediction of CV mortality, where longer arousals had more prognostic value for CV mortality than shorter arousals.

***Keywords—*** Arousals, Cardiovascular, Cardiac Intervals, Heart Rate Variability (HRV), Blood Pressure

# Acknowledgements

For thousands years, science has gradually allowed us to explore our body, to know how its different parts and systems work and to find out the complicated interactions between different organs in various conditions. Thanks to contribution of engineering and biology, we can see the human body like an integrated and cutting-edge machine operating uninterruptedly and tirelessly 24/7 as a complicated network of tens of organs and millions of cells. I should confess that how lucky I am because this research program gave me this unique opportunity to enhance my knowledge about human physiology and find out what really happens in my body, when I am sleeping. I wish this thesis could contribute even as a tiny step in the ambitious mission of humankind in discovery of themselves.

I do believe that the completion of a PhD thesis would help a student firstly to learn how to manage a research using scientific and academic methodology. Secondly, it will also assist the student to gradually feel to be an independent researcher who can create their ideas. I wish that I could achieve these two objectives.

The thesis would undoubtedly have taken its present shape due to the kindly efforts of many people. I would like to express my deepest gratitude to my supervisor Associate Prof Mathias Baumert for his continuous support of my PhD and research, immense knowledge and motivation. Without his valuable guidance in all the time of my research at University of Adelaide, I would not be able to complete this thesis.

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# List of Abbreviations

| | |
|---|---|
| AA | Autonomic arousal |
| AASM | American Academy of Sleep Medicine |
| ABPM | Ambulatory blood pressure monitoring |
| AHI | Apnoea hypopnoea index |
| AI | Arousal index |
| ANS | Autonomic nervous system |
| APG | Acceleration plethysmogram |
| BMI | Body mass index |
| BP | Blood pressure |
| BPRSA | Bivariate phase-rectified signal averaging |
| BRS | Baroreflex sensitivity |
| CA | Cardiac arousal |
| CAW | Cardiac arousal window |
| CBPE | Continuous blood pressure estimation |
| CDF | Congestive heart failure |
| CHF | Cumulative distribution function |
| COPD | Chronic obstructive pulmonary disease |
| CSA | Central sleep apnoea |
| CVD | Cardiovascular disease |
| DBP | Diastolic blood pressure |
| DN | Dicrotic notch |
| DT | Decision tree |
| DTW | Dynamic time warping |
| DW-kNN | Distance weighted k-NN |
| DWT | Discrete wavelet analysis |

| | |
|---|---|
| ECG | Electrocardiogram |
| EDS | Excessive daytime sleepiness |
| EEG | Electroencephalogram |
| EOG | Electrooculogram |
| EMG | Electromyogram |
| FN | False negative |
| FP | False positive |
| Fs | Frequency of sampling |
| GUI | Graphical user interface |
| HDS | Honest significant difference |
| HF | High frequency |
| HR | Heart rate |
| HRV | Heart rate variability |
| HT | Hypertension |
| KM | Kaplan-Meier |
| kNN | k-nearest neighbours |
| LF | Low frequency |
| LDA | Linear discriminant analysis |
| LTA | Long-term arousal |
| MA | Movement arousal |
| MAI | Movement arousal index |
| MI | Myocardial infarction |
| NREM | Non-rapid eye movement |
| N.S | Non statistically significant |
| n.u | Normalised units |
| REM | Rapid eye movement |
| RMS | Root mean square |
| OSA | Obstructive sleep apnoea |
| OSAHS | Obstructive sleep apnoea/hypopnoea syndrome |
| PASE | Physical activity scale for the elderly |
| PLM | Periodic limb movement |
| PLMA | Periodic limb movement arousal |

| | |
|---|---|
| PLMAI | Periodic limb movement arousal index |
| PLMD | Periodic limb movement disorder |
| PNS | Parasympathetic nervous system |
| PPG | Photoplethysmograph |
| PPV | Positive predictive value |
| PRSA | Phase-rectified signal averaging |
| PSD | Power spectral density |
| PSG | Polysomnography |
| PTT | Pulse transit time |
| PWA | Pulse wave amplitude |
| PWV | Pulse wave velocity |
| QDA | Quadratic discriminant analysis |
| R&K | Rechtschaffen and Kales |
| RAI | Respiratory arousal index |
| RDI | Respiratory disturbance index |
| RERA | Respiratory effort related arousal |
| RLS | Restless leg syndrome |
| RMS | Root mean square |
| RMSE | Root mean square error |
| RPSD | Ratio of power spectral density |
| SA | Spontaneous arousal |
| SAI | Spontaneous arousal index |
| SBP | Systolic blood pressure |
| SBR | Sympathovagal balance ratio |
| SCD | Sudden cardiac death |
| SD | Standard deviation |
| SDB | Sleep disordered breathing |
| SF | Sleep fragmentation |
| SFI | Sleep fragmentation index |
| SI | Slope index |
| SIPP | Slope index positive percentage |
| SNS | Sympathetic nervous system |

| | |
|---|---|
| SnorA | Snoring Arousal |
| SpO2A | SpO2 Arousal |
| LTA | Short-term arousal |
| SVM | Support vector machine |
| SWS | Slow wave sleep |
| TN | True negative |
| TP | True positive |
| TIA | Transient ischaemic attack |
| UARS | Upper airway resistance syndrome |
| VLF | Very low frequency |
| VPG | Velocity of PPG |
| 2DSW | Two-dimensional signal warping |

# List of Publications

1) Sleep arousal and cardiac time interval. S.S. Shahrbabaki, M. Baumert, Engineering in Medicine and Biology Society (EMBC), 2019 41st Annual International Conference of the IEEE.

2) Blood pressure and cardiovascular parameters during sleep arousals. S.S. Shahrbabaki, B. Ahmed, T. Penzel, D. Cvetkovic, Engineering in Medicine and Biology Society (EMBC), 2017 39th Annual International Conference of the IEEE pp.2830-2833, 2017.

3) Photoplethysmography derivatives and pulse transit time in overnight blood pressure monitoring. S.S. Shahrbabaki, B. Ahmed, T. Penzel, D. Cvetkovic, Engineering in Medicine and Biology Society (EMBC), 2016 38th Annual International Conference of the IEEE pp. 2855-2858,2016.

4) Pulse transit time and heart rate variability in sleep staging, S.S. Shahrbabaki, B. Ahmed, T. Penzel, D. Cvetkovic, Engineering in Medicine and Biology Society (EMBC), 2016 38th Annual International Conference of the IEEE, pp. 3469-3472, 2016.

5) Automatic detection of sleep arousal events from polysomnographic biosignals. S.S. Shahrbabaki, C. Dissanayaka, C.R. Patti, D. Cvetkovic, Biomedical Circuits and Systems Conference (BioCAS), 2015 IEEE, pp. 3469-3472, 2015.

6) Application of random forest classifier for automatic sleep spindle detection, C.R. Patti, S.S. Shahrbabaki, C. Dissanayaka, D. Cvetkovic, Biomedical Circuits and Systems Conference (BioCAS), 2015 IEEE, pp. 3469-3472, 2015.

7) Sleep onset detection with multiple EEG alpha-band features: comparison between healthy, insomniac and schizophrenic patients, C. Dissanayaka, D. Cvetkovic, C.R. Patti, S.S. Shahrbabaki, B. Ahmed, Biomedical Circuits and Systems Conference (BioCAS), 2015 IEEE, pp. 3469-3472, 2015.

# Chapter 1

# Introduction

This chapter begins with a general introduction to polysomnography and basics of sleep staging. The next section is a background of sleep arousals where the literature is reviewed in terms of the nature and origin of sleep arousals, how to score and classify them, what is the role of arousals in sleep fragmentation, why detection of arousals is important and how arousals are associated with different sleep disorders. Then, a background of blood pressure measurement and cardiac time intervals are presented. The previous works on cardiac timing and sleep analysis is also briefly discussed. The motivations, rationale and the structure of the thesis are then discussed. The research objectives are outlined in the last part of the chapter.

## 1.1 Polysomnography

Overnight **polysomnography (PSG)** involves typically a multitude of physiological signals such as electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), electrocardiogram (ECG), air flow, respiratory effort, chest and abdominal movement, blood oxygen saturation through fingertip photoplethysmograph (PPG). PSG systems are non-invasive and causes minimal patient discomfort. The data are collected over a night of sleep and a sleep technician then scores sleep events such as respiratory episodes or sleep arousals.

**Electroencephalography** is a method to measure electrical potentials at the surface of the scalp, caused by electrical activity of neurons in brain. This neuron electrical activity results in potential differences across different locations on the surface of the brain [1]. In terms of rhythmic activity, EEG is divided into frequency bands: delta (0.5- 4 Hz), theta (4-7 Hz), alpha (8-15 Hz), beta (16 - 31 Hz) and gamma (32+ Hz). Three EEG channels are

usually required for a PSG recording [2].

**Electromyography** is the measurement of electrical potentials caused by muscles. EMG is therefore a signal, which is controlled by the nervous system and is depended on the anatomical and physiological properties of muscles [3]. A typical PSG recording system usually requires at least one EMG channel which is obtained from the chin to measure submental activity. Chin EMG can be used to differentiate REM from NREM stages. Indeed, EMG activity decreases significantly during REM stages. EMG electrodes may also be utilised to detect periodic limb movement events.

**Photoplethysmography** is a non-invasive, convenient and cheap method to determine the variations of blood volume and blood flow in the body which occur with each heartbeat. The PPG reflects the blood movement in the vessel in a wave-like motion. In fact, it measures the relative absorption or reflection of red light and infrared across the finger [4]. The PPG signal is composed of a pulsatile component (AC) which is related to pulsating arteries and arterioles and a relatively slow varying component (DC) that represents the constant absorption of non-pulsatile tissue within the light path [5]. PPG signals have been traditionally applied to measure blood pressure, oxygen saturation, cardiac output [6]. The PPG waveform morphology also indicates whether blood vessel narrows or widens. One fingertip PPG sensor is usually used during a typical PSG recording for real-time oxygen desaturation measurement. PPG recording has also been analysed to assess autonomic functions during the sleep [4, 7]. PPG derivatives can reveal more precise details about PPG characteristics [6, 8]. The first derivative of PPG indicates the velocity of blood detected in the finger. Thus, PPG first derivative represents velocity of PPG (VPG). Likewise, the second derivative of PPG represents the acceleration of blood in the finger and can be considered the "Acceleration Plethysmogram" (APG) (Figure **1.1**). The following equations show how to compute VPG and APG:

$$VPG[n] = \frac{1}{2T}(PPG[n+1] - PPG[n-1]) \tag{1.1}$$

$$APG[n] = \frac{1}{2T}(VPG[n+1] - VPG[n-1]) \tag{1.2}$$

where $T$ is the sampling interval and equals the reciprocal of sampling frequency and $n$ is the data sample.

APG characteristics ($a$, $b$, $c$, $d$ and $e$ waves) have been utilised to determine the degree

of arterial stiffness and also to investigate whether ageing is associated with arterial stiffness [9].

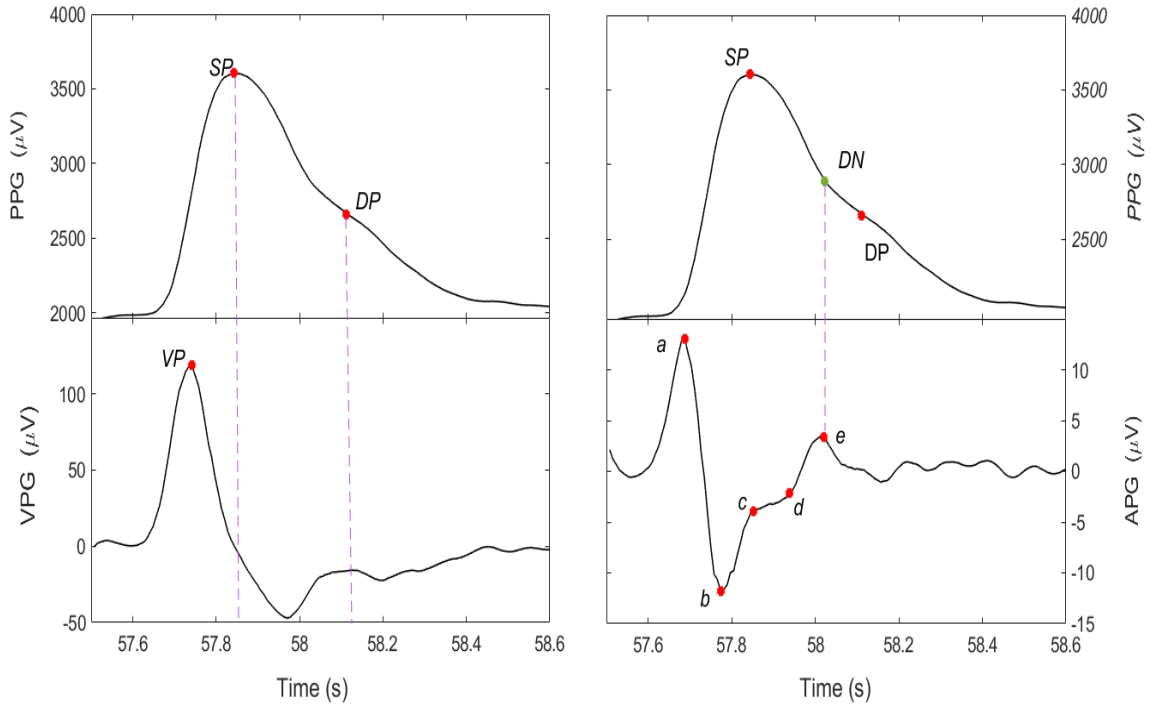



**Figure 1.1:** (**Left**) PPG waveform (top) and its first derivative (*VPG*) where *SP*, *DP* and *VP* represent systolic, diastolic and VPG peaks. (**Right**) The PPG waveform and its second derivative (*APG*), where *DN* indicates dicrotic notch. The APG waveform also consists of five waves (**a**, **b**, **c**, **d** and **e** waves).

## 1.2 Sleep Stages

According to the American Academy of Sleep Medicine (AASM) criteria, sleep is divided into two broad types [10, 11], Rapid eye movement (REM) and non rapid eye movement (NREM) sleep which constitutes to three stages (NREM1, NREM2, NREM3) as follows:

**NREM1**: This stage is the transition to sleep and known as light sleep. During this stage, eye movement is slowing down and brain produces more alpha and theta waves.

**NREM2**: During this stage, the brain begins to produce two characteristic waveforms, sleep spindle and K-complex. The spindles are rapid bursts while K-complex is the largest wave in the EEG of healthy human being.

**NREM3**: This stages is also known deep sleep or slow wave sleep (SWS). During this stage, delta wave is dominant.

**REM**: This stage is also known as active sleep due to eye movement. During REM, the brain become more active and dreams may occur.

Both, NREM and REM occur in alternating cycles, each lasting approximately 90-100 minutes, with a total of 4-6 cycles. In general, in the healthy young adult, NREM sleep accounts for 75-90% of sleep time (3-5% stage N1, 50-60% stage N2, and 10-20% stages N3). REM sleep therefore, accounts for 10-25% of sleep time. Hypnogram is a graph that shows different sleep stages as a function of time.

## 1.3 Sleep Arousals

Arousal conventionally refers to a temporary intrusion of wakefulness into the sleep [12]. In other words, arousal may indicate at least a sudden transient elevation of the vigilance level. Where the vigilance can be defined as the alertness and the attentiveness for whatever may occur [13]. Arousals may reoccur once per minute and be characterised as immediate and abrupt changes in EEG frequency during sleep [14]. Arousals usually do not lead to complete awakening, only shifting from a deeper sleep stage to a shallower one can be considered as an arousal [15]. Sleep can be fragmented by very short arousals throughout the sleeping period. These short arousals are usually ignored in sleep analyses, but their impact is significant [16].

Arousals are normally accounted as a part of normal sleep and rarely result in awakening, but when the frequency of occurrence increases, they can affect the sleep process. As a consequence, the night sleep can become highly disturbed and excessive daytime sleepiness (EDS) can occur in the following days or weeks [17]. EDS is usually used to describe a symptom of many sleep disorders such as narcolepsy, obstructive sleep apnoea/hypopnoea syndrome (OSAHS), central sleep apnoea (CSA), upper airway resistance syndrom (UARS), restless leg syndrome (RLS) and periodic limb movement disorder (PLMD). The number of sleep arousals is a predictive of daytime sleepiness [17]. More arousals lead to more fragmented sleep and consequently more somnolence and daytime sleepiness. Hence, sleep arousal index is considered as one of the markers of sleep quality which is independent of traditional sleep quality markers such as sleep efficiency and sleep latency [18]. There is also a correlation between arousal and sleep fragmentation [17]. Sleep fragmentation (SF) is the term used to describe brief awakening or arousals from sleep which are less than 15 seconds long and often occur without the awareness of

the sleeping subject [19]. SF can be quantified by sleep fragmentation index (SFI) which is defined as the number of awakening during the sleep and correlated with the frequency of arousals longer than 10s in one hour of sleep [20, 21]. Sleep arousals may add to sleep fragmentation and this results in the lower quality of sleep and daytime fatigue.

### 1.3.1 Arousal Scoring

Arousal scoring takes a significant role in sleep studies and the diagnosis of different sleep disorders. Sleep technicians and researchers mostly manually score arousal episodes based on the AASM guideline and also look for simultaneous pathological events for arousals classification.

According to the AASM criteria, EEG arousal is an abrupt shift in EEG frequency which may include theta, alpha and band frequencies greater than 16 Hz excluding spindles [10]. The EEG frequency shift must be 3 seconds or greater in duration to be scored as an arousal. The 3-seconds duration has been chosen as the minimum length for an arousal due to methodological reasons, whereas shorter arousals may have pathological significance [11]. Arousals can be scored from frontal, occipital and central EEG derivations; however frequency changes associated with arousals are more typically noted in the central and occipital derivations [2]. Figure **1.2** shows how a typical arousal can appear in EEG and chin EMG signals

### 1.3.2 Classification of Arousals

Classification of arousals has always been controversial due to the different definition of arousals and various methods for their detection [22]. Arousals can hierarchically classify into two different broad groups: cortical and sub-cortical arousals [23].

**Cortical Arousals** resulted from neurons activation in the pons and activates the cerebral cortex. They also can propagate to the cerebral cortex and are detectable in EEG and/or sub-mental EMG depending on the sleep stage [14]. Cortical arousals are associated with an abrupt shift in EEG frequency and cause an increase of high frequency power in the power spectrum of an EEG channel [24]. Apnoea/ hypopnea events or periodic limb movement episodes can induce cortical arousals [25].

**Sub-cortical Arousals** or **Autonomic Arousals (AA)** are mostly associated to different levels of central nervous system activation. Despite arousal by the basic definition refers to cortical activation, somatosensory and auditory stimulation during sleep may cause

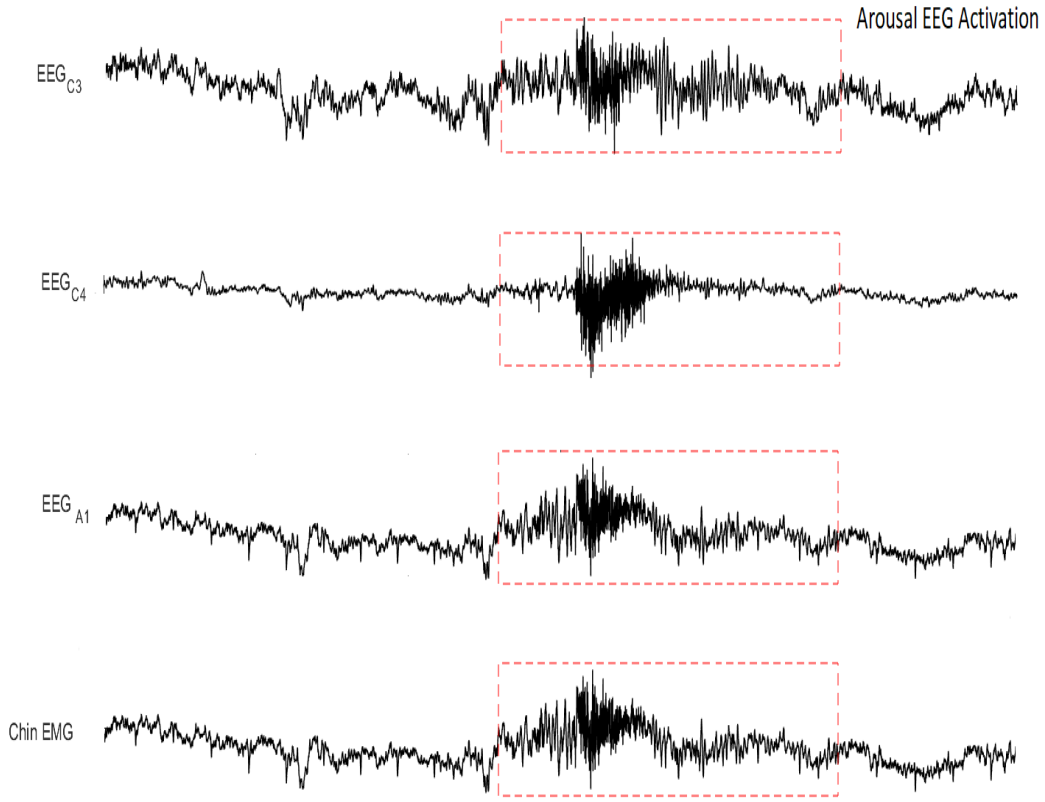



**Figure 1.2:** Arousal activation demonstrated in three EEG channels and chin EMG.

cardiac, respiratory and somatic modifications without overt EEG activation [12]. This can be interpreted as partial arousal response that can appear even without any EEG response. Hence, sub-cortical arousals can refer to all range of arousals resulted from those inducing reflex motor responses and autonomic activation to the appearance of slow-wave EEG activities such as delta bursts and K-complexes [23]. Autonomic arousal results higher level of cardiac and respiratory activity in comparison with both sleep before the arousal and relaxed wakefulness subsequent to the arousal [26]. The change in cardio-respiratory activity during the arousal has been observed in several researches. Some authors speculated the variability in cardiac functioning during AA may be associated with heart disease [27], though some authors suggested it is correlated with a reflex activation of cardio-respiratory system [26]. Furthermore, sub-cortical arousal is associated with sympathetic activation and consequently causes changes in autonomic markers like heart rate (HR), respiratory rate and blood pressure (BP) [18]. By this means, autonomic markers can be applied for detection of autonomic arousals, particularly in children. EEG activation and presence of cortical arousals are poor marker of sleep deprivation in children in contrast to adults [28]. Cortical

arousals in children are associated with significant heart rate accelerations, which typically precede arousal onset by several seconds [29]. Analysis of HR pattern can provide more significant information about sleep deprivation in children than EEG-based techniques. The major distinction between cortical and sub-cortical arousal is their effect on sleepiness. While cortical arousals are correlated to sleepiness level according to the AASM criteria, there has not been convincing evidence that autonomic arousals exhibit the same correlation [14]. Although sub-cortical arousals can influence on autonomic activation such as heart rate and respiratory rate, they would not make sleep deprived. Even there has been a considerable debate as to whether the appearance of EEG slow-wave activity and K-complexes is an indicator of a partial arousal process [23].

#### 1.3.2.1 Classification of Cortical Arousals

Detection and classification of sleep arousal may help to diagnose sleep disorders and determine the severity of sleep fragmentation. Whether an arousal is accompanied by a pathological episode and has diagnostic value, can be used for the classification of cortical arousals [25]. Loredo *et al.* suggested that generally there are two distinctly different types of cortical arousals, one occurs in relation to disturbances during sleep, such as apnoea/hypopnea or leg movement episodes; and the other occurs spontaneously [30]. Thus, we could generally classify arousal events into three category as following:

**Respiratory arousal** or **respiratory effort-related arousal (RERA)** occurs when an arousal is accompanied by respiratory events. RERA usually contains diagnostic information about breathing disorders like obstructive sleep apnoea syndrome, central sleep apnoea or upper airway resistance syndrome. RERAs are scored when the arousal occurs less than 5 seconds after the termination of the respiratory event [25]. The average number of apnoea/hypopnea events and RERAs per hour of sleep is called respiratory disturbance index (RDI) [31]. RDI besides apnoea/hypopnea index (AHI) can determine the severity of conditions in patients. For example, $RDI \leq 20$ indicates mild OSAHS while $20 < RDI \leq 40$ and $RDI < 40$ represents moderate and severe OSAHS, respectively [32].

**Periodic limb movement arousal (PLMA)** is associated with abrupt variation in EMG and plays a significant role in diagnosis of periodic limb movement (PLM) and restless legs syndrome (RLS). The PLMA is scored when there is an overlap of the events or when there is more than 0.5 seconds between the end of one event and onset of another event irrespective of which event (arousal or limb movement) occurs first [2, 11]. The periodic

limb movement-arousal index (PLMAI) is the number of periodic leg movements associated with an arousal per hour of sleep time [33]. The greater PLMAI can be interpreted as the severer PLMD.

If an arousal meets both respiratory and limb movement association rules, a respiratory arousal should be scored [2].

**Spontaneous Arousal (SA)**: If an scored cortical arousal does not accompany with any pathological events like RERA and PLMA, it would be categorised as SA according to the Australian Sleep Association commentary on AASM [2]. It is assumed that SA contains no diagnostic value and their origin has been unknown.

Arousal classification seems to be somehow subjective and highly depends on sleep scorer, the PSG recording device and their scoring approach. Some sleep technicians prefer to define new types of arousals based upon the association between occurrence of arousals and various pathological events may take place during the sleep. Events such as oxygen desaturation, heart rate acceleration or even snoring have sometimes been applied by some sleep technician during manual sleep scoring to define new classification for arousals. For instance, once an arousal episode is accompanied and associated with snoring event, it can be called snoring arousal. Likewise cardiac arousal indicates an arousal event accompanying with sudden heart rate acceleration. However, there is lack of scientific evidence for these types of arousal, their origin and their impact on sleep fragmentation. More studies are required to clarify the role of cortical and sub-cortical arousals in heart rate acceleration or oxygen desaturation and vice versa.

#### 1.3.2.2 Micro-arousal

The term of micro-arousal refers to any transient increases in the EEG frequencies in NREM sleep in the conjunction with the followings: decrease of amplitudes, disappearance of delta waves and spindles, transitory enhancement of muscle tone or phasic appearance of groups of muscle potentials, movements of the limbs or changes in body posture and transitory rise in heart rate. In REM sleep, the criteria for micro-arousals were temporary disappearance of eye movements and appearance of alpha activities [12]. Sforza *et al.* categorised micro-arousal as a cortical arousal because it originally requires EEG frequency shift [23]. The key point that differentiates micro-arousals from other types of arousal is its duration. In order to consider an abrupt EEG shift as an arousal, its duration should be at least 3 seconds. However, for micro-arousal, the minimum required length is 1 second. In other words,

any frequency shift to waking alpha rhythm with minimum duration of 1 second can be categorised as a micro-arousal episode [34].

### 1.3.3 Arousals in Sleep Disordered Breathing

Sleep disordered breathing (SDB) events can be accompanied by either a change from a deeper to lighter sleep stage or wakefulness. It means SDB events should induce respiratory arousals (RERA) that directly related to central autonomic system [7]. RERA can make sleep disturbance and cause sleep deprivation in either patient subjected to obstructive sleep apnoea/hypopnoea syndrome (OSAHS) or suffering from upper airway resistance syndrome (UARS).

#### 1.3.3.1 Arousals and Sleep Apnoea/Hypopnoea

Sleep apnoea is characterised by the pauses in breathing or infrequent breathing during sleep, lasting for at least 10 seconds. Similarly, hypopnoea is defined as a reduction in airflow or amplitude of thoraco-abdominal movement by at least 30% from baseline accompanied by desaturation of oxygen of 4% or more lasting at least 10 seconds [35]. Despite all SDB events are expected to be terminated by arousals, only 75% of them end with clear EEG arousals [36]. SDB events which are terminated with arousals are likelier to promote hyperventilation after event termination than SDB events with no arousal [37]. Thus, stimuli produce measurable cardiovascular disturbance that can sufficiently produce daytime sleepiness even without any EEG-based arousals appearing [38]. Detection of RERA provides information about whether a SDB episode terminated by an arousal or not. This information can be used for diagnosis and treatment of OSAHS. In addition, due to the association between the apnoea/hypopnea terminating and arousals induction, the arousal response is an important respiratory defence mechanism during the sleep [15]. Any impairments in the arousal response by raising the arousal threshold can increase the severity of sleep apnoea [39].

#### 1.3.3.2 UARS and Sleep Arousals

UARS is characterised by the narrowing of the airway which is associated with increasing breathing effort. UARS can cause disruptions to sleep, tiredness and daytime sleepiness [16, 40]. In patients with UARS, considerable increases in esophageal pressure (Pes), terminated by arousal can be observed. In fact, once an arousal occurs, Pes abruptly decreases which is called Pes reversal. Although, Pes reversal can be seen without the presence of a clear

arousal, Pes reversal episodes accompanied with arousals have a greater impact on ongoing respiratory effort than those Pes reversal occurring with no arousal [41].

### 1.3.4 Arousals and Periodic Limb Movement

Periodic limb movement refers to any repetitive and involuntarily leg jerks characterised by a flexion movement at ankle, knee, and hip, which arise from sleep, lasting 0.5 to 10 seconds, separated by intervals of 5 to 90 seconds, and occurring in a row of at least 4 [42]. PLMD is characterised by episodes of limb movements during the sleep [33]. PLMD should not be confused with RLS because RLS can occur while awake. In PLMD, movements are often associated with cortical arousals or awakening. The number of limb movement episodes and the periodic limb movement associated arousal (PLMA) are significantly higher in patients with PLMD in compare to RLS subjects. The index of PLMA therefore may determine the severity of PLMD. In other hand, the presence of spontaneous arousal episodes in RLS cases is more remarkable than subjects with PLMD [43]. By this means, SA index could be applied to differentiate RLS and PLMD cases.

## 1.4 Blood Pressure Monitoring

Circulating blood puts pressure on the wall of the blood vessel which is called blood pressure (BP) and expressed and interpreted in terms of the systolic blood pressure (SBP), the maximum pressure during one heart beat, over diastolic blood pressure (DBP), the minimum in between two heart beats. BP alongside with heart rate, respiratory rate, and body temperature are the four vital signs of human body. BP measurement provides useful information about cardiac output, elasticity of the blood vessel, and physiological variation [44]. High blood pressure also known as hypertension (HT), is a long-term medical condition in which the blood pressure in the arteries is persistently elevated [45]. Although high blood pressure usually does not cause symptoms, long-term high blood pressure is a major risk factor for coronary artery disease, stroke, heart failure, atrial fibrillation, peripheral vascular disease and dementia [46, 47].

Ambulatory blood pressure monitoring (ABPM) is designed to measure BP for 24h during the wake and sleep. ABPM is a known technique for HT diagnosis and usually provides BP reading every 15 minutes during the day and every 30 minutes overnight. BP in some patients abnormally increases in presence of doctor which is called white coat affect. ABPM presents more reliable BP measurement through minimising white coat effect [48].

ABPM can also provide information about BP changes after falling into the sleep. BP is expected to reduce during the sleep by almost 10-20% and this phenomenon is known as dipping. The ratio of daytime SBP over nighttime SBP called Dip ratio, can determine whether BP decreases overnight. Based on ABPM measurement and difference between night and day SBP, patients are categorised into four groups as extreme dippers ($dip \leq 0.8$), dippers ($0.8 < dip \leq 0.9$), non-dippers ($0.9 < dip \leq 1.0$) and reverse dippers ($dip > 1.0$) [49]. ABPM is an effective method in diagnosis and provide adequate and reliable data for widespread applications in medicine. However ABPM as a cuff-based method has some disadvantages which limits its application in certain clinical situations. Firstly, while cuff is being used for measurement of continuous BP, it requires at least 1-2 minutes pause between two BP measurements due to avoid errors. Hence, the short-term changes in blood pressure cannot be detected [50]. In order to investigate whether BP changes can influence sleep architecture and make sleep fragmented, short-term BP variations are essential and should not be ignored. Secondly, the inflation of the cuff may disturb the patient and the consequences of these disturbances are alterations of the BP [51]. Particularly during the sleep, cuff inflation may behave as an arousal stimulation disturb the sleep and consequently, results BP elevation. It seems cuff-based methods are not effectively reliable for sleep analysis. Hence, development of an alternative approach for a continuous, non-invasive and measurement of BP has been highly desirable [51, 52, 53]. Continuous blood pressure estimation seeks to non-invasively measure BP in real-time, continuously and without any interruptions.

There is a strong interdependence between sleep disordered breathing and HT [54]. A study showed almost 60% of OSAHS patients had HT, whilst 30% of hypertensive adults suffered from obstructive sleep apnoea [55]. Sleep disruption has been shown as a main factor of blood pressure increasing during the sleep [56]. Sleep quantitative parameters like sleep efficiency and sleep latency have association with HT. Patients with HT often suffer from short sleep duration, less REM sleep and lower sleep efficiency [57]. In addition, the lower percentage of SWS or deep sleep may increase the risk of HT [55].

### 1.4.1 Baroreflex

The baroreflex or baroreceptor reflex is a homeostatic mechanism which is responsible to maintain BP at nearly constant levels through a rapid negative feedback loop. The elevated blood pressure reflexively causes the heart rate to decrease and also causes blood pressure

to decrease. As a consequence, the decreased blood pressure decreases baroreflex activation and causes heart rate to increase and to restore blood pressure levels [58]. Baroreceptors are present in the atria of the heart and vena cava, but the most sensitive baroreceptors are in the carotid sinuses and aortic arch. The artificial stimulation of the carotid sinus or aortic arch baroreceptors by either mechanical or electrical means can produce immediate and profound electroencephalogram (EEG) synchronisation that are independent of BP changes [59, 60]. The produced EEG waves appear identical with those seen during spontaneous sleep arousals [60]. The baroreceptor effects on sleep and sleep arousals may be produced by action on a specific inhibitory centre in the brain stem known as the solitary nucleus (SN). Certain neurons in this region are known to mediate the fall in heart rate and blood pressure caused by baroreceptor stimulation [60, 61]. Baroreflex or baroreceptor sensitivity (BRS) is a measurement to quantify how much control the baroreflex has on the heart rate. BRS during the sleep in OSA patients was shown to be depressed, but improved after treatment with continuous positive airway pressure (CPAP) [62].

## 1.5 Cardiac Time Intervals

### 1.5.1 Cardiac Cycle

There are four chambers in human heart, the upper two chambers are called atria while the two lower known as ventricles. Two large veins carries poor oxygenated blood from lower and middle half of body (inferior vena cava) and upper half of body (superior vena cava) into the right atrium. Then the collected blood will be pumped in to right ventricle as soon as atria contracts. At the next step, the low oxygenated blood will be sent to the lung by passing through pulmonary artery after ventricles contracts. In other side, high oxygenated blood is being pumped from lung into left atrium through pulmonary vein. The contraction of atria brings blood down into left ventricle through passing mitral valves. The ventricle contraction also pumps blood from left ventricle to aorta to be sent to the whole body. This cycle is usually known as cardiac cycle and conducted by electrical impulses sent by sinoatrial node located in atria and makes upper heart chambers (atria) to contract. Similarly AV node manages ventricles to contract.

### 1.5.2 ECG Morphology

The electric impulse generated from sinoatrial node, spreads across the atrium, then to the atrioventricular node and through the ventricles of the heart. The impulse conducts four heart chambers to relax and contract. Electrocardiography is the process of measurement of electrical activity of heart. ECG provides detailed information about heart and consists of three main waveforms as following:

**P wave**: The depolarisation of right and left atrium results atrial contraction which appears as P wave. The early and late part of P wave represent the electrical activity generated by the right and left atrium, respectively. While the middle part of P indicates the completion of right atrial activation of initiation of left atrium activity [63].

**QRS Complex** : The complex is constituted of three waves Q, R and S. The QRS complex is the main spike seen at ECG line and corresponds depolarisation of left and right ventricles as well as contraction of ventricles (Figure **1.3**). The morphology of QRS complex may vary case by case. Even each QRS complex do not have necessarily all three waves. The convention is the Q wave is always negative, while the R wave is upward and positive. The S wave is the first negative deflection after R wave. The length of normal QRS complex is 60 to 100 ms in adults.

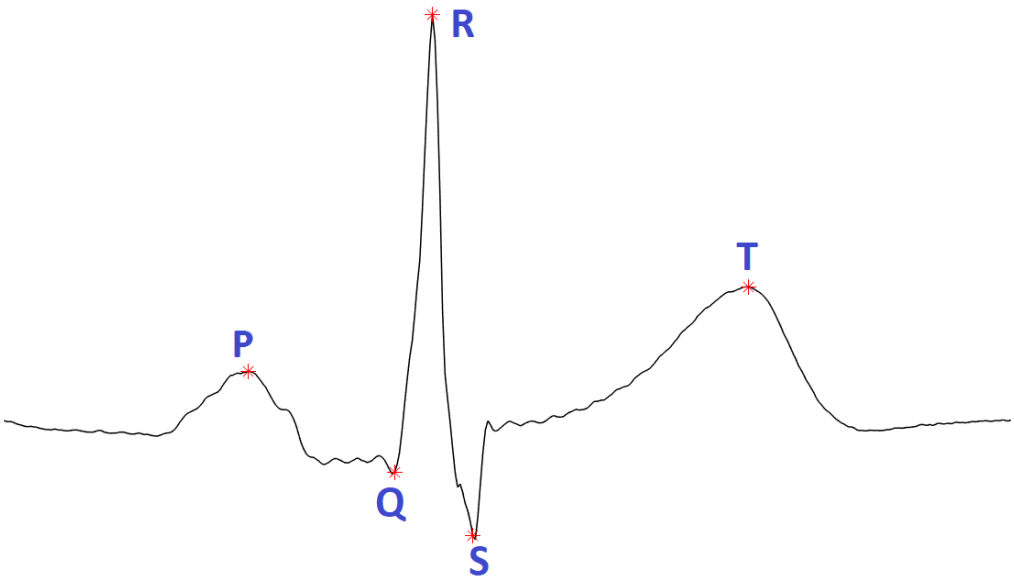



**Figure 1.3:** A typical ECG waveform with its components including **P**, **Q**, **R**, **S** and **T** waves.

**T Wave** follows QRS complex and represents ventricular repolarisation or electric recovery of ventricles. The direction of T wave is normally as same as QRS complex. T

wave inversion refers to when the direction of T is the opposite of QRS. Inverted T wave can be a sign of cardiac pathology.

A small wave between T and the P wave of next atrial repolarisation (***U wave***) has been observed in some individuals. The source of U wave is still unknown.

### 1.5.3 ECG Time Intervals

ECG time intervals can reveal the duration of each stage of the cardiac cycle. The PR interval demonstrates the time required for electric impulse to move from atria through the AV node, bundle of His, bundle branches, and Purkinje fibres until the ventricular depolarisation [63]. The normal range for PR is 120-200 ms. QT interval indicates the time required for ventricular repolarisation or ventricular recovery. In other words, QT interval approximates the time interval between the start of depolarisation and the end of repolarisation of the ventricular myocardium [64]. RR time interval also represents the time delay between two consecutive heart beats. The maximum resting RR interval for a normal heart beat (60-100 bpm) is about one second. RR time interval are reversely related with heart rate, hence the faster heart rate will result the shorter RR interval.

The variability of QT interval plays a key role in prediction of cardiac arrhythmia. QT prolongation may intensify the risk of ventricular fibrillation and cause sudden cardiac death [65]. A precise and integrated interpretation of the variability of QT intervals can therefore, provide more reliable analysis. Some methods for correction QT have been suggested. Firstly in 1920, Bazett developed a formula [66] to correct the measured QT interval to a value ($QT_c$) attributable to a heart rate of 60 beat per minute (bpm) as follows:

$$QT_c = \frac{QT}{\sqrt{RR}} \tag{1.3}$$

where ($QT_c$) is called the QT interval corrected for HR and $QT$ and $RR$ time intervals both should be in seconds.

Bazzet's non-linear formula has been often used due to its simplicity, though it obviously performs over-correct at high heart rate and under-correct at low heart rate [67]. Some alternatives have been recommended for it. For instance, Fridericia proposed to use cube root of RR interval instead of square root as follows [68]:

$$QT_{cf} = \frac{QT}{\sqrt[3]{RR}} \tag{1.4}$$

### 1.5.4 Cardiac Timing and Sleep Analysis

SDB episodes can trigger autonomic nervous system responses. Hence, cardiovascular variables such as blood pressure, heart and respiratory rate change immediately. Patients suffering from obstructive sleep apnoea (OSA) are in increased risk of some cardiac problems from heart failure to stroke. Kasai *et al.* showed that OSA exposes the cardiovascular system to intermittent hypoxia, oxidative stress, systemic inflammation, exaggerated negative intrathoracic pressure, sympathetic over-activation, and elevated BP. These can result in the progression of heart failure [69]. It has been highly desirable to understand the behaviour of various cardiovascular parameters during sleep events. Apnoea events by definition should be accompanied with significant oxygen desaturation that consequently will force cardiac system to response and cause transient changes in heart rate or blood pressure. Detection and monitoring of changes of cardiovascular measures during sleep may facilitate the diagnosis and treatment of sleep disorders.

Several studies have been conducted in terms of cardiovascular dynamics during sleep, nevertheless mainly focused on temporal and spectral features of heart rate variability (HRV). Roche *et al.* developed a model with high sensitivity based upon the time-domain analysis of heart rate variability as a tool of screening in OSAHS patients [70]. Furthermore, HRV spectral analysis and fractal mathematics also revealed a distinction between apneic and non-apneic epochs. The ratio of low frequency to high frequency spectral components ($LF/HF$) and fractal dimension of apnoea episodes with various duration are significantly different from normal sleep episodes [71]. Although Penzel urges that the surrogate pattern derived from HRV cannot replace the markers which directly extracted from respiratory recording like apnoea/hypopnoea index (AHI) for diagnosis of OSA [72].

The changes in cardiac time intervals has been discussed in the literature. Gillis *et al.* claimed that RR time interval prolonged profoundly during apnoea events in compare to normal events and decreased after apnoea hyperventilation [73]. Their observations also showed QT time interval was prolonged at the onset and during the apnoea. Whilst it shortened abruptly during the post-apnoea hyperventilation period. Moreover, sleep arousals, regardless of their type can lead PR time interval to prolong and QT and RR intervals to shortened [74].

Barr *et al.* introduced the QT interval dispersion ($QT_d$) factor regarding to Bazett's formula as the difference between maximum and minimum of corrected QT ($QT_c$) [75].

The QT dispersion ($QT_d$) is a noninvasive method to measure inhomogeneity of ventricular repolarisation or recovery times. Dursunoglu and his colleagues applied $QT_d$ to determine the severity of OSA disorder [76]. They found a strong positive correlation between AHI and $QT_d$ in non-hypertensive OSA patients.

## 1.6 Rationale

There is a perception that people who suffer from excessive daytime sleepiness (EDS) believe that they have a healthy overnight sleep but in fact their sleep is disturbed. EDS can be a symptom of factors and sleep disorders such as narcolepsy, idiopathic hypersomnia, sleep apnoea or a circadian rhythm sleep disorder. EDS affects more than 10% of the Australia's population [77] and people who suffer from EDS are at the risk of having motor vehicle and work-related accidents [78]. A considerable percentage of patients who suffer from various sleep disorders are inadequately treated because they are unaware about their condition. Once the frequency of arousal occurrence increases, sleep architecture can be affected and sleep will be fragmented. In other words, certain sleep arousals can cause sleep fragmentation and this results in the lower quality of sleep and daytime fatigue or somnolence. Sleep sufferers often complain about insufficient proper daytime functioning due to somnolence. Overall, repeated arousals in OSAHS cases may result in sleep fragmentation and consequently poor sleep quality [15]. AASM defined an international standard for manual scoring and AASM criteria are generally being used by sleep specialists and technicians in the diagnosis of sleep disorders. However, manual sleep scoring is a time-consuming process, subjective and suffers from low inter-rater agreement [79]. Hence, developing an algorithm for automatic detection and classification of sleep arousal with higher accuracy has always been desirable for sleep scientists. Despite several software have been developed for sleep analysis, they rarely can detect sleep events or classify different type of sleep arousals. Some researcher have suggested new automatic and semi-automatic methods for detection of sleep arousals, however their efforts mostly have been focused on respiratory arousals [25, 80, 81]. Arousals regardless of their type may result sleep disturbance, all arousal types were, therefore, considered in our analysis and we did not focus on a particular type of arousal and exclude the other types. Our initial goal was to develop an algorithm to automatically detect arousal episodes without consideration of their type. By this means, we could differentiate arousal and non-arousal epochs (Chapter **2.1**).

Autonomic activation during the sleep such as BP elevation or heart rate fluctuation are capable to induce arousals. On the other side, some studies demonstrated that arousal inducing can make a transient shift in BP [82] or HRV [83]. Repeated arousals not only influences on BP during the sleep, but also it may result sustained increase in daytime BP [21]. Autonomic cardiovascular parameters such as HR and BP are regulated by autonomic nervous system (ANS). Sleep arousal like an stimulator trigger ANS to make a transient change in autonomic parameters. The link between autonomic activation and EEG changes during arousal manifests a common generator located in brainstem can generate both cerebral and cardiovascular variations [84]. The analysis of BP and HR variability before, during and after arousal can therefore reveal how ANS interacts with cardiovascular system during arousal occurrence. In addition, the HR and BP changes to the induced arousal can be interpreted as the cardiovascular response to sleep fragmentation. By this means, we could describe how sleep fragmentation affects on cardiovascular system. Different aspects of the association of autonomic activation and EEG shift during arousals have been discussed in different studies [4, 18, 26, 85, 86, 87]. According to the literature, sleep arousal and sleep fragmentation are both associated with different cardiovascular of peripheral activation, however whether this association differs in various types of arousal has rarely been investigated. In fact, the type of an arousal indicates whether this arousal induces with any sleep events or arousal induced solely from cortex. Thus, cardiovascular parameters variability in different arousal types demonstrates whether adjacent activation to arousal such as apneic, oxygen desaturation or periodic limb movement episodes are related to upcoming autonomic activation. We extracted pulse transit time (PTT) from ECG and fingertip peripheral PPG biosignals and then analyse them along with arterial systemic BP and spectral components of HRV in different arousal types before and after arousal to find out the impacts of arousal types on autonomic cardiovascular parameters (Chapter **2.2**).

Sleep staging is an important part of sleep analysis and provides a general picture of sleep architecture. EEG recording during PSG process are the main reference for sleep staging. PSG system is an integrated and cutting-edge technology which has been effectively helpful in diagnosis of sleep disorders. However PSG is expensive and it also requires bunch of electrodes and sensors to be connected to the patient. This might be too disruptive for patients sleep. Therefore, PSG is restrictively used in specialised hospital-based sleep laboratory and suffers difficulty in wider application like home nursing [88]. A simpler,

reliable, low-cost and preferably wearable surrogate with the minimum number of electrodes will facilitate sleep home screening. In this thesis, we presented our effort to develop a new algorithm for sleep staging based upon PTT and HRV analysis (Chapter **2.3**). The suggested method only requires one ECG channel and one fingertip PPG sensor and can be implemented for as a wearable technology for sleep screening.

Due to significance of continuous BP, tens studies have been done to develop a non-invasive method which can estimate BP continuously and uninterruptedly. According to the literature, PTT is known marker of continuous BP measurement [51, 44, 53, 89]. PPG first and second derivatives (VPG and APG) can indicate another interpretation of PPG morphology characteristics [6]. As mentioned in 1.1, APG has mainly been applied for arterial stiffness assessment [9, 90] whilst PPG first derivative (VPG) has rarely been undertaken in the literature. In Chapter **3**, a new empirical approach was suggested and evaluated based upon the analysis of first and second derivatives of PPG for PTT estimation. Then, the performance of VPG and APG in continuous overnight BP measurement were compared.

Sleep arousal causes sudden changes in cardiovascular and respiratory system. Arousal is also capable to instigate cardiac arrhythmias in subjects with a susceptible myocardium [91]. Higher number of arousals in patients suffering from obstructive sleep apnoea (OSA) is likely to intensify accompanying cardiac pathology [91, 92]. Furthermore, OSA and is known as an independent risk factor for cardiovascular disease [93]. The probability of Sudden cardiac death (SCD) amongst OSA patients at night is considerably higher in contrast to the general population [92]. Cardiac autonomic activity during the sleep is mainly studied through HRV analysis. Beyond HRV, QT and PR time intervals are another cardiovascular markers which have been investigated in some studies for analysis of cardiac system either in sleep or wake [91, 94, 95]. According to the literature, QT variability is correlated with the severity of OSA and surprisingly this correlation is stronger than HRV [94]. It seems that QT can take a similar role like RR in analysis of cardiovascular system during the sleep. Arousal occurrence seems to be likelier to make QT and RR shortened than lengthened [91]. However this provides no information about the instantaneous changes in cardiac intervals right before and after arousal occurrence. In addition, whether arousal type, duration or sleep stages can make a significant difference in QT and RR interval variability is still unknown. It seems necessary to find out QT and RR correlation and inter-relation before and after arousal occurrence. Whether QT and RR interval variability

are associated with arousal index, sleep fragmentation or the degree of OSA, allows us to assess the diagnostic significance of cardiac intervals in different sleep disorders. In Chapter 4 of this thesis, we investigated different aspects of cardiac time intervals during the sleep arousal.

Cardiac time intervals variability and severity of OSA are correlated. As mentioned, OSA sufferers are more prone to cardiovascular disease. In Chapter 5, an analysis on the association of QT and RR interval variability during arousal and subject's physical and medical background have been presented. We also investigate whether QT and RR cardiac variability during arousal have prognostic value for cardiovascular mortality.

## 1.7 Objectives

The general objective of this thesis is to present a comprehensive study about sleep arousal and its effect on dynamics of cardiovascular system.

### 1.7.1 Primary objectives

The manuscript also specifically focuses on the following primary objectives:

- Develop an algorithm for automatic detection of sleep arousals.
- Detect sleep stages using HRV and PTT analysis.
- Estimate cardiac time intervals before and after arousal onset to monitor cardiac intervals variability during arousal episodes.
- Study the effect of arousal type, duration and sleep stages on QT and RR interval variability.
- Study the association between arousal related cardiac intervals variability and human subjects' physical characteristics and medical history.

### 1.7.2 Secondary objectives

In addition, the study is going to focus on following secondary objectives:

- Explore the relationship between the sleep arousal occurrence and the changes in various PSG bio-signals including PPG, ECG, EEG and EMG.
- Investigate on the relationships between arousal and cardiovascular variables such as heart rate variability, systolic and diastolic blood pressure and pulse transit time.

- Develop a method for the estimation of overnight continuous blood pressure using PPG derivatives.
- Analyse instantaneous changes in QT and RR intervals prior to and following arousal occurrence.
- Investigate on the association of cardiac intervals variability with sleep fragmentation and the severity of sleep apnoea disorder.
- Assess the capability of arousal-related cardiac intervals variability in prediction of cardiovascular mortality.

# Chapter 2

# Sleep Arousals and Cardiovascular Variables

## 2.1 Automatic Detection of Arousals

### 2.1.1 Background

As discussed in the previous chapter, arousal is characterised by a sudden increase in EEG frequency lasting between 3-15 seconds. Detection of sleep arousals plays a critical role in sleep studies and provides valuable information for diagnostic purposes. Manual arousal scoring is still widely accepted and routinely applied for clinical and research purposes. Sleep technicians often conduct manual scoring according to AASM guideline [11] in order to visually mark and distinguish sleep disorder events like arousals. Needless to say that manual scoring is subjective, time-consuming and has low inter-scorer agreement. Thus, investigation onto the development of a technique for automatic detection of arousals has always been desirable.

In 1999, De Carli and his colleagues applied two EEG channels (F4-C4 and C4-O2) alongside with submental EMG to design an automatic arousal detector using wavelet analysis [80]. It was one early attempt to find a computerised alternative for manual scoring. Basner *et al.* developed an ECG-based algorithm for automatic arousal detection [79]. Their aim was to design an automatic model, which is able to differentiate between cortical and autonomic arousals. The changes of heartbeat, emerged in R wave of ECG signal, during the sleep arousal was the fundamental of their algorithm for detection and classification of sleep arousals. However, the accuracy and sensitivity of the model was low for arousals

longer than 10 seconds. In another study, various PSG bio-signals such as EEG, chin and tibialis EMG in addition to airflow pressure and temperature were employed to detect cortical arousal in subjects with sleep apnoea syndrome. The developed technique could detect RERA by 86%, nonetheless, movement and spontaneous arousals were not considered [25]. Sorensen *et al.* proposed an algorithm for arousal detection in healthy adults and patients with Parkinson disease. Extracted features from spectral analysis of EEG and submental EMG plus the hypnogram data used as the input of an artificial neural network. The algorithm could identify arousal events from non-arousal events by sensitivity of 88%. Since the hypnogram data was extracted manually, the algorithm could not be accounted as a fully-automatic novel for arousal detection [81].

The aim of this preliminary study was to develop an algorithm for automatic detection of sleep arousals. In this stage, we only investigated how to analyse different PSG biosignals to distinguish arousal events and did not consider the type of arousal as well as sleep disorder groups.

## 2.1.2 Methodology

***Subjects***: Nine subjects' overnight PSG recordings which have been performed at St Luke's Hospital (Sydney, Australia) were analysed for this study. Six subjects were males whilst three were females and their age range was 34-69 years. Four subjects suffered from moderate and severe OSAHS, one diagnosed with PLMD and four subjects were identified healthy and without any sleep disorders.

### 2.1.2.1 Data Acquisition

For each subject, 8-hour clinical sleep PSG recordings were undertaken with the sampling frequency of 256 Hz using Bio-Logic System and Adults Sleepscan Vision Analysis (Bio-Logic Corp, USA). The recording montage signals consisted of: EEG (C3-A2, C4-A1 and O2-A1), left and right EOG (EOG-L and EOG-R), submental EMG, ECG, leg movement actigraphy, nasal and oral airflow, snoring sound, saturation oxygen and chest and abdomen breathing effort. The sleep stages were visually scored at 30s epochs according to Rechtchaffen and Kales criteria [96]. Sleep arousals as well as respiratory and limb movement events were also scored by an independent sleep expert according to the AASM criteria. The detailed information about manual arousal scoring has been presented in Table **2.1**. The Arousals index was calculated as the number of arousals per one hour sleep.

| *Subject ID* | *Total Sleep Time (h : m)* | *No. of Arousals* | *Arousal Index* | *No. of RERA* | *No. of PLMA* | *No. of SA* |
|---|---|---|---|---|---|---|
| 1 | 7 : 02 | 520 | 74.0 | 381 | 27 | 112 |
| 2 | 6 : 16 | 45 | 6.6 | 0 | 17 | 28 |
| 3 | 7 : 16 | 314 | 43.3 | 108 | 89 | 117 |
| 4 | 6 : 21 | 273 | 43.0 | 0 | 151 | 122 |
| 5 | 8 : 12 | 137 | 16.7 | 7 | 85 | 72 |
| 6 | 5 : 27 | 147 | 27.0 | 51 | 67 | 30 |
| 7 | 5 : 18 | 64 | 12.1 | 3 | 42 | 19 |
| 8 | 6 : 37 | 74 | 11.2 | 1 | 30 | 43 |
| 9 | 6 : 59 | 121 | 17.1 | 15 | 63 | 43 |
| Mean±SD | - | 188.3±145.6 | 27.9±20.6 | 62.9±117.4 | 63.4±39.2 | 65.1±39.3 |

**Table 2.1:** Partial descriptive analysis of PSG data, including manual scoring of different types of arousals (respiratory effort related arousal (*RERA*), periodic limb movement arousal (*PLMA*) and spontaneous arousal (*SA*)).

### 2.1.2.2 Data Pre-processing

Figure **2.1** presents a schematic diagram of proposed model for automatic arousal detection. We applied various signal processing and statistical method for development and evaluation of suggested arousal detector.

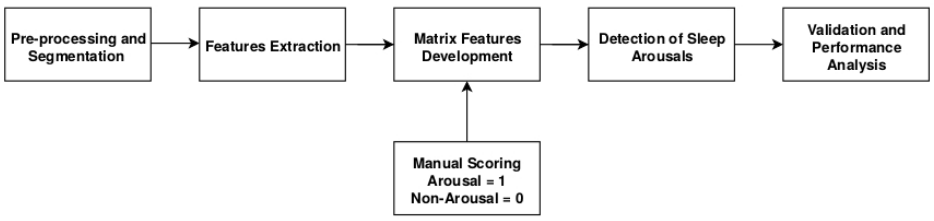



**Figure 2.1:** Schematic diagram of arousal detection model

According to AASM criteria, both central and occipital EEG channels can be used for scoring of sleep arousals. Submental EMG is also required manual scoring during REM sleep stage. Hence, the analysis of three channel EEG and submental EMG seem to be essential for detection of arousals. Sleep technician did sleep scoring independently to this study. Their strategy for classification of arousal was the association of sleep disorder episodes and arousal occurrence. Thus, scored arousals were classified into RERA (Figure **2.2)** or PLMA (Figure **2.3**) whether the arousal was associated to respiratory or periodic

limb movement. Otherwise, it was classified as a spontaneous arousal event. Moreover, arousal episodes shorter than 3 seconds were excluded in this study.

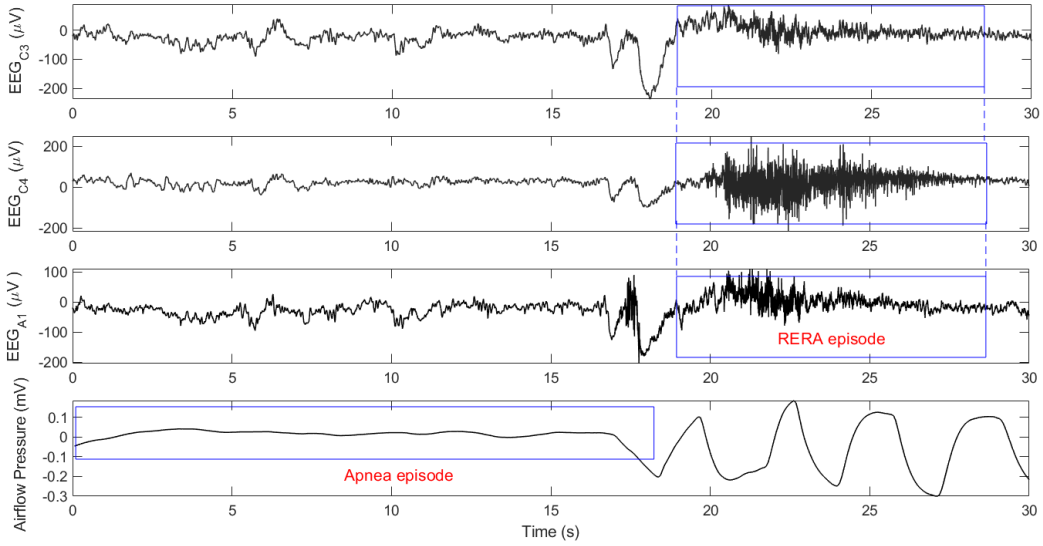



**Figure 2.2:** The apnoea episode terminated by a RERA episode.

In actual clinical diagnosis, only arousals which are related to pathological events have crucial meaning. Vice versa, spontaneous arousals have less diagnostic value because they are not related to any pathological events [25]. Other PSG biosignals such as ECG, leg movement and airflow reveal information about pathological events like heart rate acceleration, apnoea/hypopnea or body movement episodes. This information therefore could be beneficial for detection and particularly classification of different types of arousals.

To develop the algorithm, we analysed two central EEG channels (C3-A2 & C4-A1), one occipital EEG channel (O2-A1), submental EMG, leg movement actigraphy, airflow time series and ECG. All signals were segmented into 30 seconds epochs and the algorithm was going to differentiate epoch with arousals from no-arousal epochs. In fact, once an arousal occurs during an epoch, it can make sudden changes emerging in different PSG biosignals based on the type of arousal. We hypothesised that PSG extracted features of an epoch with an arousal would be significantly different from an epoch without presence of any types of arousal.

### 2.1.2.3 Feature Extraction

In order to develop feature extraction model and then feature matrix, various signal processing methods were applied and 32 features were extracted for each 30-second epoch as

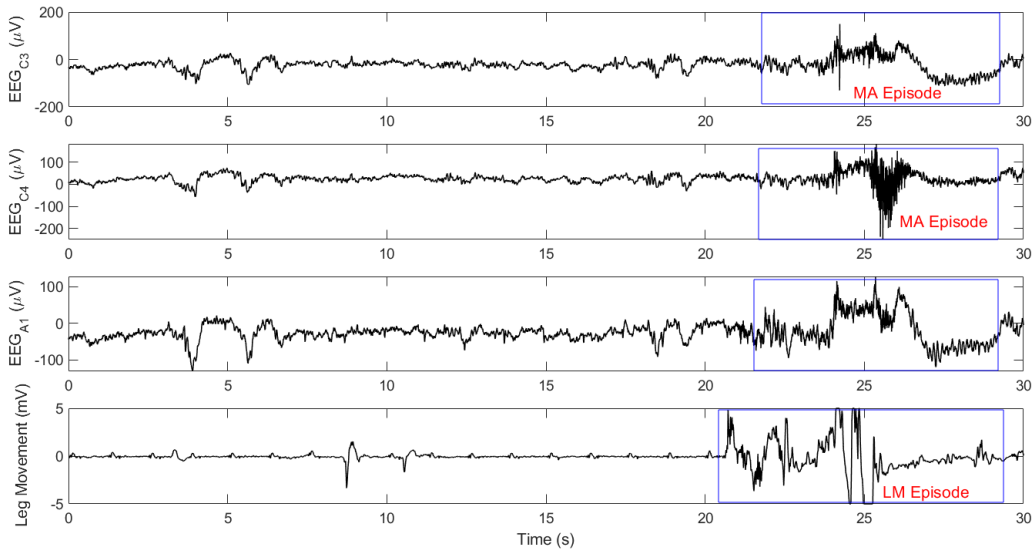



**Figure 2.3:** A periodic limb movement arousal (PLMA) accompanied with a PLM event

follows:

**EEG features**: Once three EEG channel biosignals were segmented into epochs, two different approaches were applied to extract EEG features. The first approach for EEG features extraction was to estimate percentage of EEG bands or relative power bands. The second was to compute the ratio of previous and current time windows.

**Relative EEG power bands**: All epochs were band-pass filtered through a Butterworth filter with second order cut-off frequency from 0.4 to 40 Hz. Then each epoch was transformed to the frequency domain using Welch's algorithm [97]. The outcome was a vector of power spectral values in frequency range from 0 to 128 (the half of sampling frequency). The vector of power spectral values was then categorised to EEG bands according to the frequency bands: delta band (0.5 to 4Hz), theta band (4 to 8Hz), alpha band (8 to 15 Hz), beta band (16 to 32 Hz) and Total band (0.4 to 40 Hz). The ratio of sum of absolute values of each particular band to the summation of total band is considered as the relative power band [98]. For instance, the delta relative power for *k-th* epoch $(p_k^{\delta})$ was computed as follows:

$$p_k^{\delta} = \frac{\sum_{f=0.4}^{f=4} P_f}{\sum_{f=0.4}^{f=40} P_f} \times 100\%. \tag{2.1}$$

Similarly, theta, beta and alpha relative power for three EEG channel recordings were computed and consequently 12 features were created.

**Ratio of previous and current time windows**: Sleep arousal is characterised as a

sudden shift in EEG frequency consisting of alpha, beta and theta activity. Sudden shift is associated with intensive variations in EEG energy before and after occurrence of sleep arousals and can be calculated by power spectral density (PSD). Since sleep arousals are corresponded to greater frequencies such as alpha and beta than delta, in this stage all EEG epochs were being passed through a band-pass filter with cut-off frequency from 8 to 40 Hz. Within each epoch, a time window with duration of 10 seconds before the moment was applied. Indeed, the past 10-second window represents the EEG activity in advance to a particular moment. In a similar way, the EEG activity for following initial moments can be monitored by a current 3-second window. PSD in each window [81]:

$$PSD = \frac{\sum_{i=1}^{n} X(i)^2}{N}, \tag{2.2}$$

where $X$ is the filtered EEG signal segment transformed to the frequency domain and $N$ is the number of samples in the Fourier transformed segment. The ratio of PSD of 3-second (current) and 10-second (previous) is called ratio of PSD (RPSD) and indicates frequency changes at each moment. Three features such as minimum and maximum of RSPD in addition to area under RPSD curve of each epoch for three EEG channels were computed and totally 9 features were extracted.

**EMG features**: Submental EMG signals were segmented to 30-second epochs and then filtered through a 2-order high-pass filter with 30 Hz frequency of cut-off in order to remove unnecessary frequencies and artefacts. The first feature is root mean square (RMS) of EMG that represents the EMG epochs amplitude:

$$RMS = \sqrt{\frac{x(i)^2}{N}}, \tag{2.3}$$

where *x(i)* is the EMG epoch time series and $N$ is the number of samples.

In addition, EMG time series were transformed into frequency domain using Welch's method. The mean of power spectral values and MNF (Equation **2.4**) were calculated as two more EMG extracted features [99]:

$$MNF = \frac{\sum_{j=1}^{M} f_j P_j}{\sum_{j=1}^{M} P_j}, \tag{2.4}$$

where $f$ and $P$ is frequency and power spectrum values of bin $j$ and $M$ is the length of frequency bin.

**Leg movement feature**: The RMS of leg movement time series was calculated and considered as an extracted feature for each epoch. This feature represents limb movement and can be useful for detection of movement arousals.

**Respiratory feature**: Once airflow time series was segmented into epochs and transformed into spectral domain, three features such as arithmetic mean, standard deviation, peak amplitude (PA) were computed. PA is the maximum of power spectral values [100].

**Heart rate features**: The R peaks of ECG signals were detected according to the Murthy *et al.* algorithm [101]. Heart rate (HR) were computed through QRS complex locations and used for feature extraction. Four statistical moments including mean, standard deviation, skewness and kurtosis were calculated for HR and stored as HR extracted features.

**Feature matrix**: For each subject, a feature matrix was developed with $n$ rows as the number of sleep 30-second epochs and 33 columns. The first 32 columns were allocated to the normalised features and the last column determined whether the epoch was manually scored as an arousal epoch or not associated with any types of sleep arousals. This column were being used in training and validation.

#### 2.1.2.4 Development of Classifier

A classifier was required to differentiate epochs with arousals from non-arousal epochs. The k-nearest neighbours (kNN) is a simple and suitable classifier model for clustering and it is capable to be used for both regression and classification purposes. A kNN classifier developed was applied on feature matrix to distinguish epochs with arousals. The ratio of arousal to non-arousal epochs varied subject by subject and it might affect on the performance of the classifier. In subjects with higher ratio, all arousal and non arousal epochs were considered for classifications. However in subjects with lower number of arousals, for each arousal epoch, two non-arousal epochs were randomly chosen to avoid imbalance of datasets in classification.

#### 2.1.2.5 Performance Analysis and Validation

In order to evaluate the performance of classifier, we computed three statistical measures, sensitivity, specificity and accuracy. They were calculated as following:

$$Sensitivity = \frac{TP}{TP+FN} \times 100\%, \tag{2.5}$$

$$Specificity = \frac{TN}{FP+TN} \times 100\%, \tag{2.6}$$

$$Accuracy = \frac{TN+TP}{TP+FP+TN+FN} \times 100\%, \tag{2.7}$$

where

*TP* = Number of arousals detected which matched with the actual events;

*FP* = Number of arousals detected which did not match with the actual ones;

*TN* = Number of non-arousal events which matched correctly;

*FN* = Number of non-arousal events which did not match correctly. We also applied Leave-one-out cross-validation method to assess the validation of our algorithm. Eight subjects' features matrices were selected for training and one subject's matrix was left for testing step, with the same process being repeated for remaining tested subjects. By this means, we could investigate whether suggested model was successful in arousals detection.

### 2.1.3 Results and Discussion

The performance analysis of algorithm in detection of sleep arousals was summarised in Table **2.2**. The higher sensitivity indicates the model could accurately distinguish greater number of arousal epochs. Likewise, the higher specificity demonstrates that model was more successful in detection of Non-Arousal epochs. The accuracy also reveals the preciseness of developed classifier model in arousal detection.

| Subject ID | Sensitivity(%) | Specificity(%) | Accuracy (%) |
|---|---|---|---|
| 1 | 93.8 | 71.9 | 85.4 |
| 2 | 77.8 | 100 | 98.7 |
| 3 | 67.5 | 97.1 | 86.5 |
| 4 | 87.9 | 96.9 | 93.7 |
| 5 | 70.1 | 99.1 | 95.0 |
| 6 | 78.9 | 98.2 | 93.9 |
| 7 | 79.7 | 99.5 | 97.5 |
| 8 | 79.7 | 98.6 | 96.8 |
| 9 | 75.2 | 98.3 | 94.9 |

**Table 2.2:** Performance of Algorithm using Leave-One-Out-Cross-Validation method.

The average sensitivity, specificity and accuracy were 79.0%, 95.5% and 93.6%, respectively. The algorithm could classify sleep epochs into arousal epochs and non-arousal epochs by high accuracy and sensitivity. The algorithm was able to detect arousal epochs in two subjects with sensitivity greater than 85%. According to the Table **2.1**, the *Subject 1* suffered from severe OSAHS with extremely massive number of RERA (n = 381). The sensitivity and accuracy for this case was 93.9% and 85.4%, respectively. On the other hand, the *Subject 4* was diagnosed as a PLMD patient due to 151 PLMA scored during their overnight sleep. We could automatically detect arousal epochs in this subject with accuracy of 93.7% and sensitivity of almost 88%. It indicates that the algorithm performance in differentiation of arousal epochs from non-arousal was independent of subjects' disorders and types of induced arousals. Based upon over observations, the algorithm did not perform well in *Subject 3*, where the achieved sensitivity was 67.5%, despite of high accuracy by 86.5%. In this case, majority of respiratory arousals was overlapped or surrounded by periodic movement and spontaneous arousals. This causes the detector model failed to distinguish a considerable number of arousal epochs. We only focused on the detection of arousals without considering their types, as a result, it would not classify arousals based on their association with pathological events.

In this study, the aim was to investigate whether PSG extracted features were capable in automatic detection of sleep arousal episodes. The purposed algorithm generally could differentiate arousal epochs from non-arousal epoch with sensitivity of about 80% and tremendously high accuracy (95.5%). Sugi *et al.* have been done a similar study previously [25], however our approach in feature extraction and classification was different from them. Their focus also on detection of RERA, whilst we never excluded other types of arousals such as PLMA and SA. Unlike to Sorensen *et al.* study [81], no manual scoring parameters were involved in development of our model. Then, this model should be considered as a fully-automatic technique. The suggested algorithm can be improved and upgraded for classification of cortical arousals. Furthermore, since various PSG biosignals from EEG and submental EMG to airflow and ECG, were being analysed and involved in this study, an extensive range of features were generated. This feature extraction strategy can therefore be used for further sleep analysis, particularly, when the goal is to monitor the overall performance of physiological system during the sleep.

### 2.1.4 Conclusion

The developed algorithm based upon features extracted from PSG biosignals and kNN classifier could automatically detect arousal epochs and distinguish from non-arousal epochs with high accuracy and sensitivity. The study was preliminary and only 9 subjects' PSG datasets were analysed. A dataset with larger sample size would help to reach a robust automatic algorithm. The developed algorithm can be improved and implemented as an automatic surrogate for manual sleep event scoring.

## 2.2 BP and Cardiovascular Parameters During Sleep Arousals

### 2.2.1 Background

The autonomic nervous system is responsible for regulation of variables such as heart rate, blood pressure, body temperature and respiratory rate. Sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) are two main branches of autonomic nervous system. SNS stimulates the body for "fight or flight" response which refers to body's physiological reaction to a perceived attack, threat, danger or harmful events. During a sympathetic activation, different autonomic parameters are affected by SNS. For instance, HR increases and blood vessels narrows (vasoconstriction) in order to restrict blood flow which consequently leads to BP increases. Despite BP and HR responses to arousal weakens by the age, the ventilatory response is independent of the age [102]. On the other hands, PNS is responsible for stimulation "rest-and-digest" or "feed and breed" activities that occur when the body is at rest [103]. A fundamental component of the PNS is vagal tone or vagal activity which is related to the vagus nerve and results in different effects such as HR reduction, vasodilation/constriction of vessels, glandular activity in the heart, lungs, and digestive tract [104].

Sleep arousals can result to a shift in sympathetic activation and therefore, lead to peripheral vasoconstriction [18]. Due to close association of cardiovascular parameters like HR and BP with sympathetic activities, a transient arousal can affect these markers. Vasoconstriction induces changes in blood flow and volume represented in PPG signal [6]. Thus, PPG can be used as a marker of finger vasoconstriction [105]. Delessert and his colleagues claimed that a sudden drop in PPG pulse wave amplitude (PWA) are associated with arousal occurrence. In other words, a significant increase in EEG power density in all EEG frequency bands was found during PWA drops ($p < 0.001$), whereas EEG did not shift considerably before and after PWA drop [4]. PWA reduction occurs even in absence of visual scored arousal, hence PWA drop can be considered as a sign of arousal occurrence. Moreover, the combination of PPG features (PWA and Area under PPG curve) has been shown as an robust detector of arousals with high accuracy [7]. PPG-based algorithms could distinguish autonomic arousals which sometime does not appear in EEG signal and seems to be undetectable through EEG analysis. Fingertip PPG has also been used alongside with

ECG to measure pulse transit Time (PTT).

Pulse transit time generally refers to the time delay between two arterial sites. PTT is defined as the time taken by the arterial pressure wave to travel from the aortic valve to the periphery is recorded as the time delay between the ECG R-wave and the arrival of the corresponding PPG pulse wave at the fingertip [106, 86, 107, 108]. In addition, the term of pulse arrival time (PAT) has also been used in some recent studies to describe the time taken for a pulse wave to travel from the heart to periphery [109, 110]. In this thesis, to avoid confusion, only PTT was used to as the time delay between two arterial sites (**Figure 2.4**). PTT has been mostly utilised for continuous BP measurement [44, 51, 53]. In addition, it has been indicated as a reliable marker of OSA episodes and arousals, particularly in children [111, 86, 112]. Hence, it can be claimed that PTT is a suitable measure of autonomic activities either in wake or sleep.

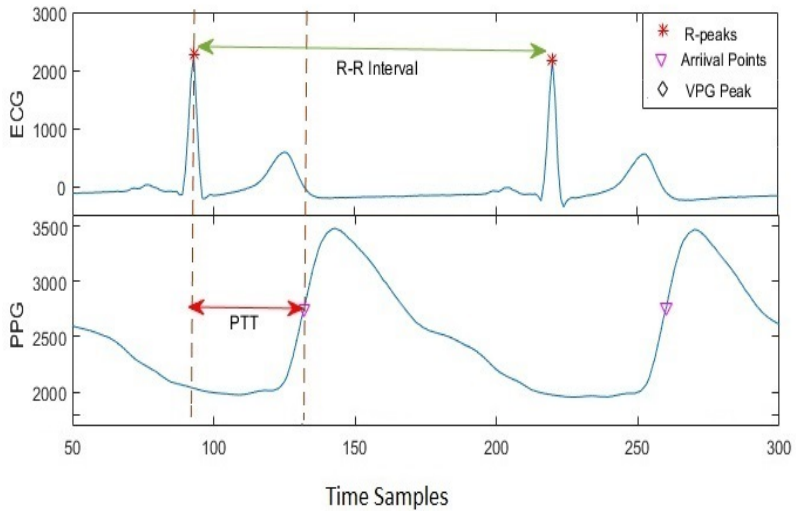



**Figure 2.4:** Graphical demonstration of R-R interval and PTT estimation. PTT is pulse transit time from R wave to the 50% of the pulse amplitude.

It is believed that any arousal episodes, may produce a small sudden rise in BP [113]. A study statistically compared three effective indices in sleep fragmentation including apnoea/hypopnoea index (AHI), EEG arousal index and blood oxygen saturation as well as three autonomic markers consisting BP, PTT and HR. It demonstrates that PTT and BP are more sensitive than HR in detection of arousals [114].

Heart rate variability (HRV) refers to variation of heart rate in beat-to-beat intervals. HRV spectral analysis reveals a quantitative scale of cardiovascular function as well as sympathetic/parasympathetic interaction [115]. HRV spectral analysis produces three frequency

bands. These bands are known as very low frequency (VLF) for 0.0033-0.05 Hz, low frequency (LF) for 0.05-0.15 Hz, and the high frequency (HF) for frequencies 0.15-0.5 Hz. The term of vagal tone is also used to assess heart function. During the rest and in absence of any external triggers, sinoatrial pacing generally maintains the heart rate in the range of 60–100 beats per minute (bpm) [116]. Both SNS and PNS work together to increase or slow the HR. The vague nerve controls vagal tone modulation through acting on the sinoatrial node and slowing its conduction. Due to vagal tone impact on HR, it can be indirectly measured through heart rate variability (HRV) [117]. HF of HRV reflects vagal modulation [118, 119] while the ratio of LF/HF power may estimate the ratio between SNS and PNS activity under controlled conditions [120]. The term of sympathovagal balance ratio (SBR) has been used in several manuscripts to describe LF/HF [121, 122, 123].

Sforza *et al.* applied HF and LF spectral components of HRV to determine the degree of sleep fragmentation. Their research indicated that the ratio of LF/HF and heart-rate increment to total power spectral density (%VLFI) were extremely higher in patients with SDB and PLMD in compare to insomniac subjects. Sleep deprivation in both SDB and PLMD patients are associated to the number of arousal, respiratory and limb movement events. Thus, LF/HF and %VLFI can indirectly predict the level of sleep fragmentation [85].

The aim of this study was to investigate on the relationship between sleep arousals and five cardiovascular parameters including DBP, SBP, PTT, HF and LF spectral components of HRV. We also attempted to find out how these parameters varying during and just before/after the occurrence of different arousal types.

## 2.2.2 Methodology

***Subjects***: We analysed ten subjects (6 females and 4 males with average age of 45.8 $\pm$ 11.2 years) overnight PSG recordings collected at the Center for Sleep Medicine, Charite University Hospital (Berlin, Germany). Six subjects suffered from insomnia (2 males and 4 females) whilst four subjects were healthy (2 males and 2 females).

### 2.2.2.1 Data Acquisition

PSG Data was recorded using SOMNOscreen PSG system (SOMNOscreen PM, SOMNOmedics, USA) which included 40 channel recordings. The ECG had been recorded at frequency sampling rate $(F_s)$ of 256 Hz whilst PPG recordings were sampled at $F_s$ = 128 Hz.

Existing systolic and diastolic reference blood pressure (SBP and DBP) data had been automatically calculated using analysis software, DOMINO 2.7 (DOMINO, SOMNOmedics, USA) at $F_s$ = 4 Hz. In order to achieve calibration, BP was measured by Riva Rocci sphygmomanometer method before and during the recording.

#### 2.2.2.2 Manual Arousal Scoring

Sleep arousals were manually scored by a sleep technician according to AASM criteria. Arousals were also manually classified based on whether an arousal is associated with a physiological event close-by or not. Based on their classification, once a respiratory episode either apnoea or hypopnoea induced an arousal, this type of arousal was classified as RERA. Cardiac arousal (CA) represents one associated with a heart rate acceleration or tachycardia event. Similarly, PLMA, snoring arousal (SnorA) and SpO2 arousal (SpO2A) represent arousals associated with periodic limb movement, snoring and oxygen desaturation episodes, respectively. If an arousal event was not associated to any other physiological events, it would be considered as a SA episode. Table **2.3** shows the outcome of manual arousal scoring for ten subjects.

| *Subject ID* | *No. (**SA**)* | *No. (**CA**)* | *No. (**PLMA**)* | *No. (**RERA**)* | *No. (**SnorA**)* | *No. (**SpO2A**)* | ***Total*** |
|---|---|---|---|---|---|---|---|
| 1 | 12 | 36 | 4 | 8 | 2 | 2 | 64 |
| 2 | 23 | 0 | 15 | 11 | 8 | 24 | 81 |
| 3 | 13 | 33 | 1 | 3 | 1 | 6 | 57 |
| 4 | 42 | 1 | 6 | 0 | 12 | 2 | 63 |
| 5 | 15 | 4 | 3 | 1 | 3 | 0 | 26 |
| 6 | 28 | 5 | 21 | 1 | 5 | 0 | 60 |
| 7 | 10 | 4 | 1 | 0 | 1 | 0 | 16 |
| 8 | 10 | 4 | 7 | 0 | 0 | 0 | 21 |
| 9 | 15 | 3 | 17 | 21 | 2 | 2 | 60 |
| 10 | 21 | 8 | 1 | 9 | 6 | 22 | 67 |
| **Total** | 189 | 98 | 76 | 54 | 40 | 58 | 515 |

**Table 2.3:** A description of manual scoring of different types of sleep arousals. Where *SA*, *CA*, *PLMA*, *RERA*, *SnorA* and *SpO2A* represent spontaneous, cardiac, periodic limb movement, respiratory, snoring and $SpO_2$ arousal, respectively.

#### 2.2.2.3 Feature Extraction

The ECG, PPG recordings alongside with existing SBP and DBP time series of 10 subjects were extracted from PSG datasets. The sampling rate of ECG recordings was twice of PPGs. Thus, PPG recordings had to down-sample to PPG frequency of sampling ($F_s$ = 128 Hz) at the first step. In each subject, according to scored arousal onsets, the ECG and PPG recordings 15 seconds prior and following to each onset were picked and analysed. ECG time series were then analysed for peak detection in order to extract HRV. PTT biomarker was also derived from ECG and PPG analysis.

**HRV Extraction and Spectral Analysis**: HRV data can be usually derived from beat-to-beat heart rate (Fig **2.4**). R peaks were detected using Murthy *et al.* algorithm [101]. At the next step, R-R time intervals were calculated and applied to estimate HRV. The obtained HRV had various sample rates between 1 and 1.5 Hz. Hence, it was resampled at $F_s$ = 4 Hz and then transformed to frequency domain using Welch's method [97]. LF and HF components of HRV can be computed as the normalised percentage power in the LF frequency band (0.05-0.15 Hz) and HF band frequency (0.15-0.5 Hz) [115].

**PTT Estimation**: PTT is the time taken by the pulse wave travel between two arterial sites. The first site was once ventricles depolarise and pump blood into the body and represented by R-wave and the second arterial site is known as the pulse pressure arrival point and detected using the fingertip PPG sensor. In this research the point with 50% of pulse amplitude was considered as arrival point (Fig **2.4**). Obtained PTT was also resampled at 4 Hz to adjust with SBP/DBP recordings.

**Development of Features Matrix**: Three extracted cardiovascular features as well as DBP and SBP, which had been automatically measured by software were utilised to investigate sleep arousals. Each subject's features matrices consisted of 5 rows as five features. For each single arousal, features during arousal occurrence was assigned as Arousal Matrix. Since the duration of arousals differed from one arousal to another one, the number of columns for each arousal varied either. For instance, once the duration of an arousal was 5 seconds and regarding to $F_s = 4Hz$, the Arousal Matrix would have 20 columns. In order to investigate how five cardiovascular markers changed before the arousal onset, for each single arousal, features related to 10 seconds prior to arousal onset was selected and stored as 10s-Pre-Arousal Matrix. Similarly, we developed 5s-Post-Arousal Matrix that represented features related to 5 seconds after arousal. Hence, for each single arousal three matrices

were developed.

#### 2.2.2.4 Slope Index Estimation

In order to investigate whether a particular feature was increasing or decreasing right before, during and right after the occurrence of an arousal, we created the slope index (*SI*) which can be computed through first degree polynomial regression. By this means, we could determine the behaviour of various features in different types of arousal. Figure **2.5** demonstrates how we estimated *SI* for SBP time series through polynomial regression. Whether SI was positive or negative or zero, could determine the trend of *SI* feature over time. As long as, *SI* is positive, the vector has upward trend and the feature is increasing over time. Similarly, the negative *SI* indicates a descending trend. $SI = 0$ means that the feature was unchanged over time. Regarding to three feature matrices, we computed the SI for all arousals and for all features to compare variations of SBP, DBP, PTT, LF and HF in different types of sleep arousals. At the next step, we developed a new marker, slope index positive percentage (SIPP), which calculated the percentage of arousals with a positive and ascending trend of a cardiovascular parameter. In other words, the greater *SIPP* for a particular parameter indicates the parameter is likelier to increase than decrease before or during or after an arousal event.

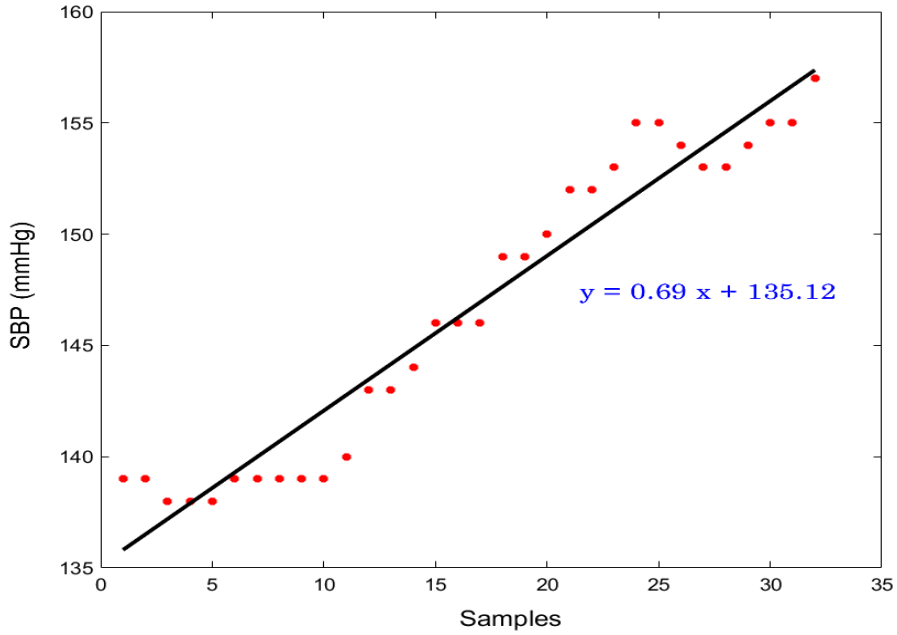



**Figure 2.5:** SBP regression diagram and Slope Index (SI) estimation.

#### 2.2.2.5 SBR Variability

For each arousal, sympathovagal balance could be obtained through LF/HF ratio for time interval before and after onset. The change rate of SBR at arousal onset ($\Delta SBR_o$) was defined as the normalised difference of SBR pre- and post-onset. This ratio determined how sympathetic activation varied in once an arousal induces. $\Delta SBR_o$ can also indicates whether the sympathetic response is depended to arousal type or not.

#### 2.2.2.6 Statistical Analysis

To visualise SIPP variabilities in various arousal groups before, during and after arousal episodes, we applied graphical analysis. The SIPP histograms allowed us to determine how cardiovascular variable behaved during arousal three time periods. The one-way ANOVA test was also applied to assess whether changes in LF, HF, SBP, DBP and PTT are depended to arousal types. The significance level ($p - value < 0.05$) determined whether various arousal types caused statistically significant changes in cardiovascular parameters.

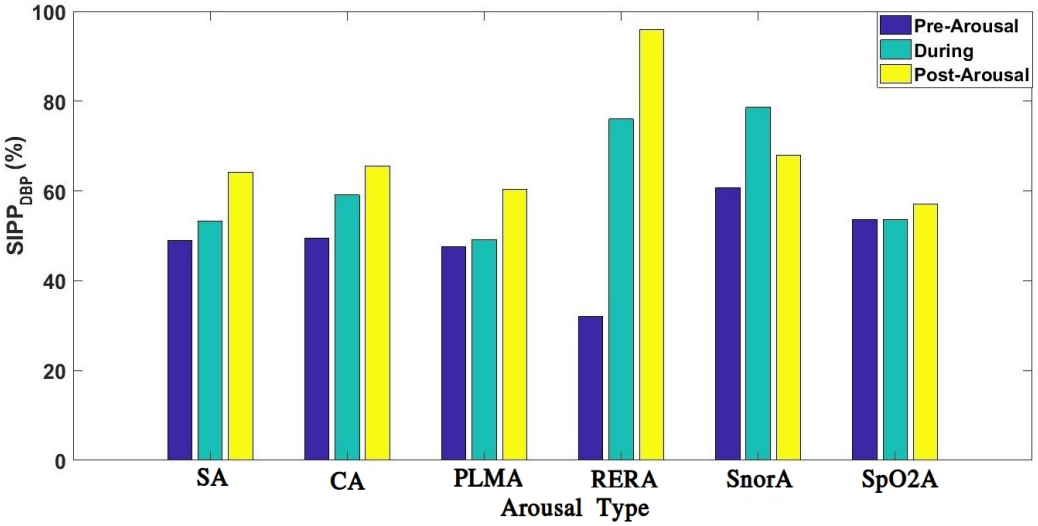
### 2.2.3 Results and Discussion

#### 2.2.3.1 Slope index analysis

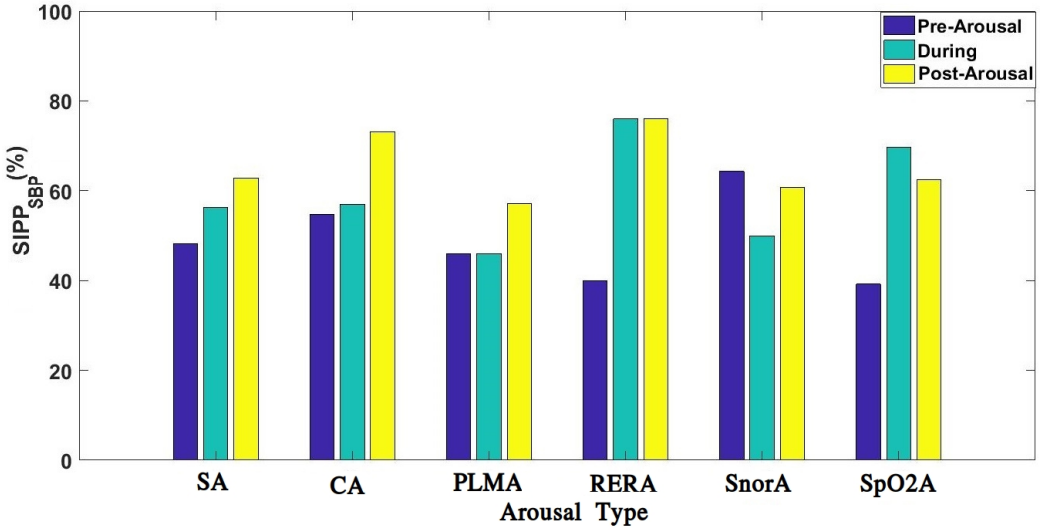
We extracted and utilised five features (DBP, SBP, PTT, LF and HF). Thus, we computed $SIPP_{DBP}$, $SIPP_{SBP}$, $SIPP_{PTT}$, $SIPP_{LF}$ and $SIPP_{HF}$ of pre-, during and post-arousal situations. The outcome of *SIPP* analysis for continuous BP measures have been shown in Figure **2.6**. $SIPP_{DBP}$ and $SIPP_{SBP}$ indicate that in how much of arousal episodes and their neighbouring moments DBP and SBP has increased. In these cases, *SIPP* indicated that the probability of a sudden rise in systolic and diastolic BP in different type of arousals.

For instance, $SIPP_{DBP}$ 10 seconds prior to spontaneous arousal was 49% (Fig. **2.6-a**) which indicates that in almost less than half of spontaneous arousals, DBP right before the occurrence of arousal had upward trend. In the other half of SA episodes, DBP was either steady or decreasing. During an SA event, the probability of DBP elevation was higher before the SA onset ($SIPP_{DBP}$ = 53%). Interestingly, five seconds after the onset of about 64% arousals, DBP was increasing. We reached very similar results for SA events in terms of $SIPP_{SBP}$ analysis. Due to the obtained result, we would not able to claim decisively about the role of spontaneous arousals in BP elevation. In addition, since SA is not related to any pathological events, its origin and nature is not very clear.

During about 78% of RERA episodes, DBP had an ascending trend. The DBP eleva-




**(a)**




**(b)**

**Figure 2.6:** Statistical analysis of slope index positive percentage (SIPP) of systolic and diastolic blood pressure in different types of arousals. Sub-figures (***a***) and (***b***) demonstrate SIPP performance of DBP and SBP biomarkers, correspondingly. Spontaneous, cardiac, periodic limb movement, respiratory, snoring and SpO2 arousals have been represented by ***SA***, ***CA***, ***PLMA***, ***RERA***, ***SnorA*** and ***SpO2A***, respectively.

tion was continuing at least 5 secs after the end of arousal in 96% of RERA events. Once we compared $SIPP_{DBP}$ in different types of arousal, only RERA and SnoreA are likely to increase DBP with high probability. Both of them are related to respiratory issues. In terms of systolic blood pressure, $SIPP_{SBP}$ analysis (Figure **2.6-b**) shows that once a respiratory arousal occurs, it is very likely to result higher SBP ($SIPP_{SBP} = 78\%$) during the arousal

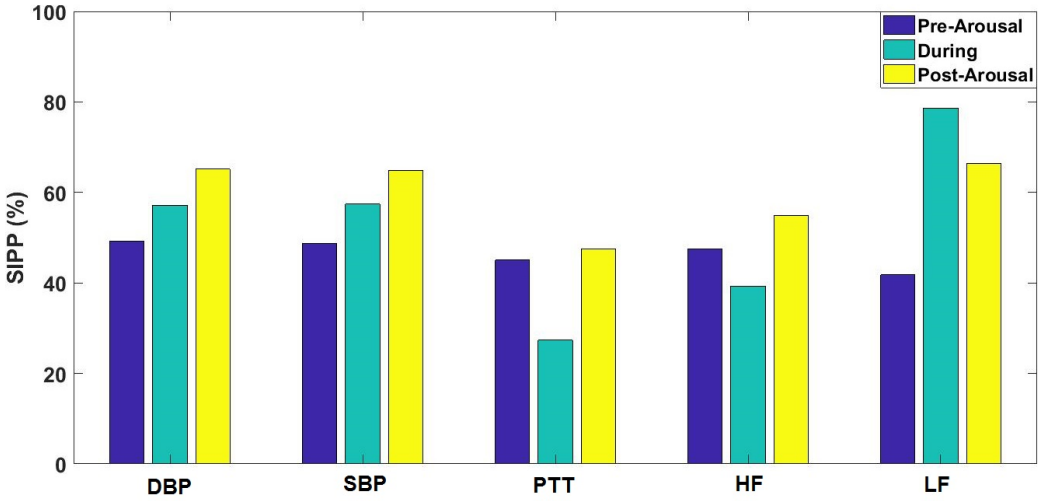



**Figure 2.7:** Performance of **SIPP** for all five cardiovascular parameters in all arousals regardless of their types.

and 5 seconds post-arousal. According to Figure **2-7** diagrams, the pre-arousal BP either in DBP or SBP increased in about 48% of all arousal types. Whilst SIPP had a small rise during the arousals to about 57%. It means once an arousal occurs, both SBP and DBP are likelier to increase than to drop. Figure. **2.6** and **2.7** indicates that respiratory events can elevate both SBP and DBP with high probability. Snoring arousals could highly impact on DBP by $SIPP_{DBP}$ = 79% during the arousal occurrence. However, this phenomenon has not been observed in SBP ($SIPP_{SBP}$ = 50%). RERA events are mostly associated to breathing problems and respiratory sleep conditions like apnoea or hypopnoea. In other words, any either abnormal low breath rate or any pauses in breathing would probably increase blood pressure. The CA episode was scored once EEG shifted simultaneously to heart rate acceleration. Both SBP and DBP are more probable to rise 5 seconds after occurrence of CA episode ($SIPP_{DBP}$ = 67% and $SIPP_{SBP}$ = 74%). In fact, a sudden heart rate increase might lead to upcoming BP elevation.

Different trends of BP before and after of onset in some arousal groups indicate the effect of arousal on blood pressure. To determine the causality of arousal occurrence and BP elevation, the temporal priority of the arousal episode to BP changes should be undertaken. In other words, sleep arousal may cause BP increases [124], not BP changes may induce arousal when the arrow of time was considered. Our findings show that arousal as a sudden EEG activation is more likely to cause sudden BP increase than decrease, but these BP changes are mostly prominent in RERA which were induced by respiratory events. How-

ever, the correlation between RERA occurrence and BP elevation may be spurious because both are the effects of SDB events.

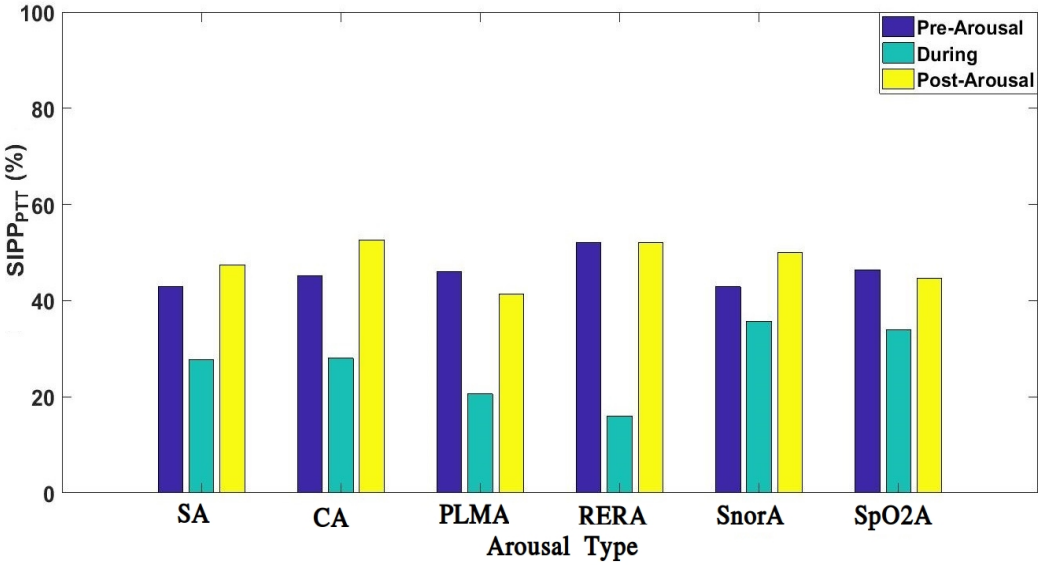
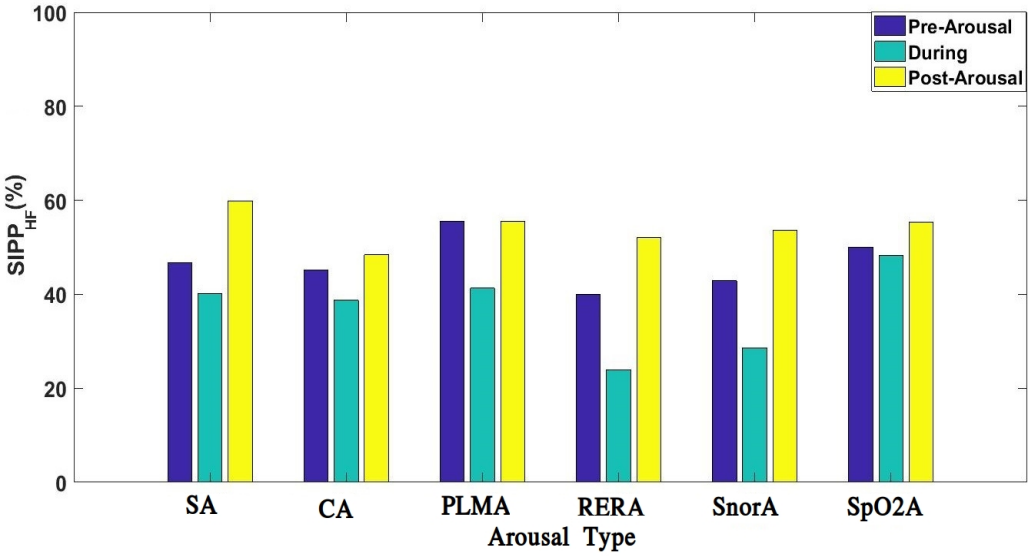


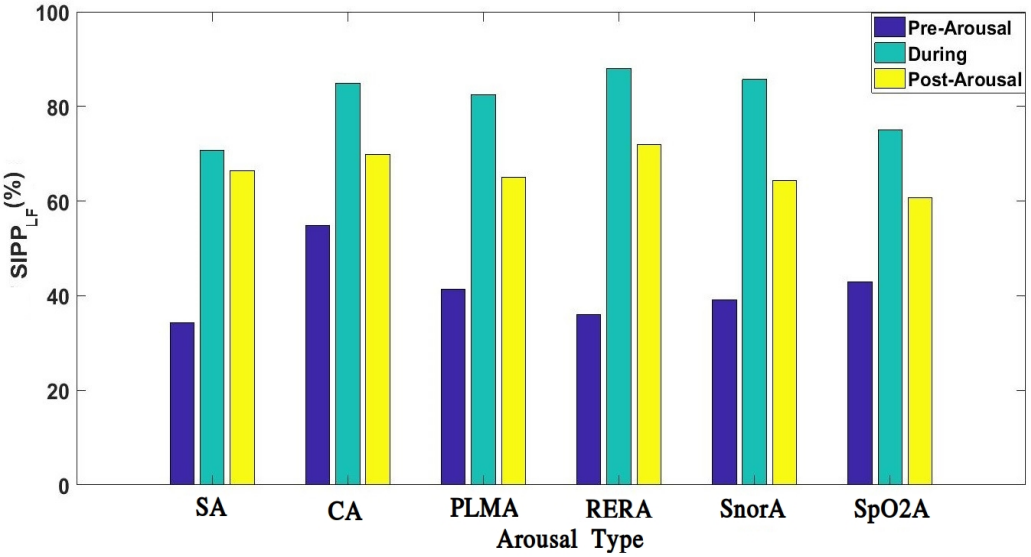

**Figure 2.8:** $SIPP_{PTT}$ performance analysis in different types of arousal.

Obtained results also show that PTT is very likely to drop once an arousal occurs (Figure **2.8**). Pre-arousal and post-arousal $SIPP_{PTT}$ were correspondingly 47.5% and 48.7%, whilst during only 27.6% of all sleep arousals, regardless of their types, a rise in PTT has happened. PTT in 85% of respiratory arousals dropped. As a consequence, it can be claimed that respiratory arousals are extremely likely to be accompanied with PTT reduction. This fact can be considered to develop a consistent and reliable marker for detection of respiratory arousals. Several research have been done formerly to investigate whether PTT is a reliable and non-invasive detector of respiratory disorder events and arousals particularly in children [111, 112, 125]. However, in this research, we found that PTT is probably dropping during arousal inducing regardless of arousal type. Although observed drop in PTT was more intense and considerable during RERA events.

In terms of HRV spectral components, we found out that LF component are very likely to increase when an arousal occur ($SIPP_{LF}$ = 80%), whereas before arousal onset in only 39% of arousals, a shift in LF power has been observed. Therefore, LF power shift can be an indicator of arousal event (Figure **2.7**). Similar to BP cases, RERA events had the greatest impact on LF by $SIPP$ = 90%. Unlike the LF component, HF band dropped during the occurrence of 61% of all arousals. About 75% of RERA events made a decrease in HF




**(a)**




**(b)**

**Figure 2.9:** $SIPP_{HF}$ and $SIPP_{LF}$ performance analysis in different types of arousal.

activity during the arousal (Figure. **2.9**). LF band is associated to the sympathetic activity while HF is related to the parasympathetic activity [115]. Since the arousal is believed as a short and transient intrusion of wakefulness into sleepiness, it triggers sympathetic activity like LF band to power.

$SIPP_{HF}$ before, during and after SpO2 arousals were roughly close and around 50%. Since SpO2As are associated with desaturated oxygen in blood, we expected their *SIPP* results should be similar to RERA events due to their dependency to oxygen level. However,

the outcome was different. The term of SpO2 arousal has been rarely referred in literature and our knowledge about them and their nature and origin is limited. Respiratory events are accompanied with oxygen desaturation. Thus if a SpO2 fluctuation event occurred in prior or next to an arousal episode, it has been mainly regarded as a consequence of respiratory event rather than an independent event. According to the manual sleep scoring, there were some arousal events which were related to oxygen desaturation without presence of any typical respiratory event. Regardless of arousal types, the increase in LF power was observed in most of arousals. This raises a question about the causality or in simpler words, arousal cause HR change or vice versa. With consideration of arrow of time, we could claim that arousal can cause transient changes in HR [126], although those alterations are more prominent in respiratory arousals.

Rahman *et al.* showed that LF and LF adjusted with respiratory are correlated with baroreflex sensitivity and reflects baroreflex function independently of cardiac sympathetic innervation [127]. According to the literature, occurrence of arousal regardless of its origin can be associated to baroreceptors reflex [60]. Our results show that in more than 80% of arousals, LF had a positive trend at arousal onset (**Figure 2.7**). Due to association of LF and BRS, we can claim that arousal occurrence could trigger baroreceptors. Once an arousal occurs, BP is more likely to elevate that can lead to baroreflex activation. The increase of baroreceptors function causes heart rate to decrease represented by high $SIPP_{LF}$ ($\geq 80\%$) to control BP and return it to normal level. However, post-arousal BP elevation continued in more than 60% of arousals for at least 5 seconds. This indicates that baroreceptors require time to regulate BP after arousal onset.

#### 2.2.3.2 Slope Index Variability and Arousal Types

To investigate whether slope index of cardiovascular parameters were associated to the type of arousal, ANOVA analysis was applied. The $SI_{LF}$, $SI_{HF}$, $SI_{DBP}$, $SI_{DBP}$ and $SI_{PTT}$ time series were evaluated pre- and post-arousal onset in different types of arousal through ANOVA test to find out whether the SI significantly differed in various arousal types or not (Table **2.4**). Post hoc Tukey's honest significant difference (HDS) test indicated the SI variability in which types of arousals were significantly different. Obtained results show the slope of LF and HF components of cardiac and spontaneous arousals were significantly different before arousal ($p = 0.03$). $SI_{LF}$ or $SI_{HF}$ determined the rate of changes in HRV spectral components pre- and post-arousal onset. Before arousal inducing, there was no signifi-

cant difference of both $SI_{LF}$ or $SI_{HF}$ between arousal groups which induced by a close-by physiological events (CA, RERA, PLMA, SnorA and SpO2A). This indicates that LF and HF fluctuations before arousal onset are independent of arousal type. In other words, pre-arousal HRV could not determine what physiological event occurred which resulted the associated sleep arousal. On the other hand, SA events only appear as EEG activation without any accompanying physiological changes. Hence, no significant physiological events like heart rate acceleration or oxygen desaturation are expected to occur prior to SA onset. This results the significant difference between CA and SA in terms of their $SI_{LF}$ or $SI_{HF}$ variability.

| Variables | | ANOVA test (p-Value) | Post hoc Signs |
|---|---|---|---|
| $SI_{LF}$ | Pre-Onset | 0.03 | CA vs SA |
| | Post-Onset | 0.001 | CA vs SA<br>CA vs SpO2A |
| $SI_{HF}$ | Pre-Onset | 0.03 | CA vs SA |
| | Post-Onset | N.S | - |
| $SI_{SBP}$ | Pre-Onset | N.S | - |
| | Post-Onset | N.S | - |
| $SI_{DBP}$ | Pre-Onset | 0.03 | RERA vs SpO2A |
| | Post-Onset | N.S | - |
| $SI_{PTT}$ | Pre-Onset | N.S | - |
| | Post-Onset | N.S | - |

**Table 2.4:** ANOVA test assessed whether changes in slope index of cardiovascular parameters before and after arousal onset are related to arousal type. Post hoc signs show arousal types with significant difference in SI time series pre- and post-arousal types.

The post-onset ANOVA assessment of $SI_{LF}$ reveals that there was a significant difference between CA vs SpO2A and CA vs SA ($p = 0.001$). While post arousal $SI_{LF}$ variability in RERA and CA events were not significantly different, $SI_{LF}$ of SpO2A had a different approach.

Pre- and post-onset $SI_{DBP}$ time series shows DBP variability before occurrence of different type of arousals. ANOVA and post-hoc HDS results show that $SI_{DBP}$ in only RERA and SpO2A were significantly difference before onset ($p = 0.03$). Different trend of DBP prior to RERA ans SpO2A episodes indicates that oxygen desaturation events accompanied with respiratory events do not have a similar effect on diastolic blood pressure as same as oxygen desaturation events which not accompanied with respiratory episodes. No significant difference was observed between arousal groups in terms of $SI_{DBP}$ and $SI_{SBP}$ means that post-arousal BP variability are independent of arousal types and sleep events which induced the arousals. ANOVA test rejected any dependency of $SI_{PTT}$ variability to arousal type.

#### 2.2.3.3 $\Delta SBR$ and Arousal Type

To evaluate how sympathetic activity changed after arousal inducing, $\Delta BSR$ was computed for arousals. The term of $\Delta SBR > 0$ means that the ratio of sympathetic activity to vagal tone increased at arousal onset. In other words, once the arousal induced, a significant shift in sympathetic activity occurred. $\Delta BRS = 0$ indicates that arousal resulted no significant changes in sympathovagal balance. $\Delta SBR < 0$ means that arousal occurrence was accompanied with a decrease in sympathetic activity in contrast to parasympathetic activation. As shown in Figure **2.10**, the majority of spontaneous and cardiac arousals resulted positive $\Delta SBR$ that refers to an increase in sympathovagal balance at onset of these arousal groups. Particularly, 80% of CA episode caused a shift in sympathetic activation. On the other hand, other arousal types such as RERA, PLMA and SpO2A mainly resulted a drop in SBR at arousal onset. The prominent negative $\Delta SBR$ in these arousal groups indicates a post-arousal higher parasympathetic activation than sympathetic activation. A respiratory event or a limb movement episode that induced an arousal is expected to shift the sympathetic activation. However, according to SBR analysis, LF/HF ratio was likelier to drop after arousal occurrence. This indicates a post-arousal reduction in sympathetic activation and an increase in vagal tone at the same time. The ANOVA analysis and post hoc test also confirmed that $\Delta SBR$ in CA and SA groups were significantly different with RERA, PLMA, SpO2A and SnorA groups ($p < 0.0001$). Figure **2.11** presents the post hoc test and shows $\Delta SBR$ variability through different arousal types. RERA, SnorA and SpO2A are symptoms of problem in breathing mechanism during sleep. Our observations manifest an increase of parasympathetic activity during these types of arousals in compare to SA and

CA. This means respiratory event are more associated with increased vagal tone. Previously, Chrysostomakis *et al.* found out that HRV parameters which reflect parasympathetic activity are increased during the night in OSA patients. [128]. They also concluded that CPAP therapy can affect on vagal tone and reduce parasympathetic activity and alleviate bradyarrhythmic episodes. According to the literature, sleep arousal is expected to result an increase in sympathetic activation and a drop in PTT [129]. However, our results indicated that respiratory arousal and even movement arousal are likelier to elevate parasympathetic activation. In addition, LF/HF ratio is depended to the sleep stage where it could reach to the maximal during REM and minimal during NREM [115, 130]. LF/HF ratio during REM is also associated to the subjects gender [115]. Hence, the difference between LF/HF ratio in various arousal types might be related to their sleep stage than its type or adjacent sleep events. Furthermore, non-stationarities increase the likelihood of finding a shift of sympathovagal balance toward sympathetic predominance and alter significantly the power of the statistical tests [131]. This may limit usage of LF/HF as a reliable marker of sympathovagal balance.

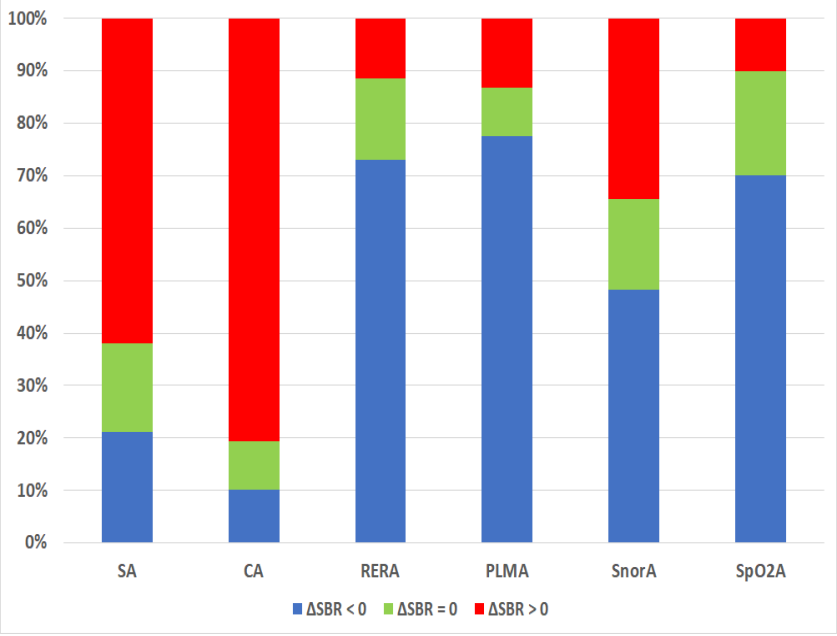



**Figure 2.10:** $\Delta SBR$ (**blue**) indicates sympathovagal balance changes at arousal onset. $\Delta SBR < 0$ represents the percentage of arousals with a drop in SBR at onset. Similarly, $\Delta SBR = 0$ (**green**) represents the percentage of arousals with no significant change in SBR. $\Delta SBR > 0$ (**red**) shows the percentage of arousals with ascending SBR at onset

### 2.2.4 Limitations

The maximum duration of an arousal episode in 15 seconds. This time length may limit estimation of LF power (0.05 - 0.1 Hz), hence 15 seconds ECG before and after arousal onset (30 second recording) were picked for HRV analysis. In this study, we only accessed to 10 subjects PSG recordings. A larger size database would help to conduct a holistic investigation on BP and HR momentary changes during sleep events.

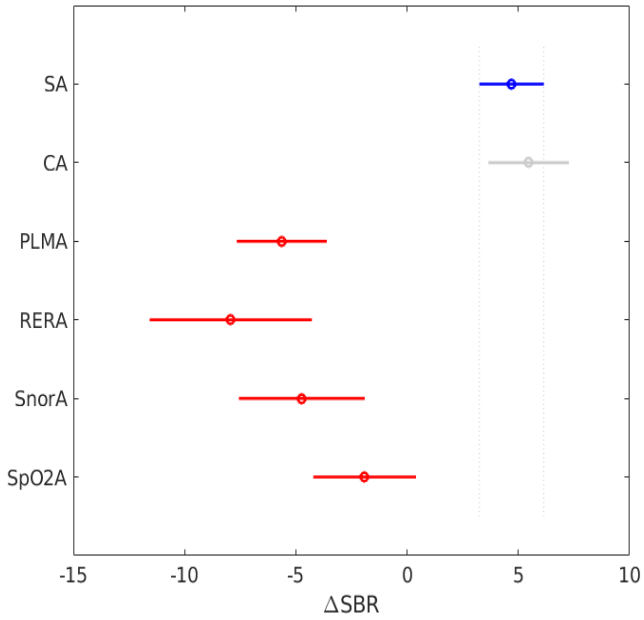



**Figure 2.11:** Post hoc tukey's HDS analysis compares the $\Delta SBR$ variability in different types of arousals.

### 2.2.5 Conclusion

In conclusion, this study demonstrated that in all types of arousals, the probability of BP increasing is greater than BP decreasing based on our results. Particularly, it is significantly likely to rise when a respiratory arousal occurs. We also found out that low frequency spectral component of HRV increased during the 78% of all arousals and 88% of respiratory arousals. This happened due to the association of LF component to sympathetic activities. Vice versa, we observed a considerable drop in $SIPP_{HF}$ during the arousal. It means that sleep arousal occurrence will be likely accompanied with HF band power reduction. Similarly, $SIPP_{PTT}$ during the arousal was lower than either before or after arousal inducing. This was more significant in respiratory arousals. As a consequence, PTT drop seems to be a reliable marker for detection of respiratory events and arousals in clinical settings.

## 2.3 Pulse Transit Time and Heart Rate Variability in Sleep staging

### 2.3.1 Background

An important step in clinical diagnosis and treatment of various sleep disorders is sleep staging. Sleep architecture includes transitions from wakefulness to shallower sleep and then proceeding to the deep sleep. Thus, identifying sleep stages provide valuable information about general architecture of sleep. Rechtschaffen and Kales firstly published their guideline of sleep staging in 1968, also known as *R&K* criteria [96]. According to *R&K* criteria, sleep stages should be scored by using EEG central leads (C3, C4) and a normal sleep is divided to five stages: Stage 1, Stage 2, Stage 3, Stage 4 and Stage REM sleep. The AASM later released their guideline for sleep stages scoring. Based on AASM criteria sleep stages can be scored through frontal, occipital and central leads. The AASM criteria modified some terms in sleep staging in compare to *R&K* where sleep is divided two main stages, REM sleep stage and NREM sleep stages (*NREM*1, *NREM*2 and *NREM*3) [11]. Both guidelines have been widely employed for manual sleep scoring that is a tedious, subjective and time-consuming process. Creating a computerised alternative that can limit technologist's involvement has always been highly desirable. In recent years, several methods for automatic detection of sleep scoring by using EEG, EMG and EOG has been developed [132, 133, 134, 135].

During transition between sleep stages, several physiological parameters associated to ANS such as heart rate, body temperature, respiratory rate and blood pressure may alter. In this study, we specifically focused on two measures of cardiac activity regulated by ANS and their relations with sleep stages HRV and PTT.

Spectral analysis of HRV provides a quantitative evaluation of the sympathetic/parasympathetic interaction [115]. Several researches investigated applying HRV features to classify the different sleep stages [88, 136]. In 2010, Yilmaz *et al.* claimed that one lead ECG was capable in determining sleep stages and the degree of AHI [136]. Their features extraction approach was based upon time statistical analysis of RR intervals and they evaluated three classification methods, k-NN, support vector machine (SVM) and quadratic discriminant analysis (QDA). The accuracy of their algorithm with k-NN, SVM and QDA classification were 68.9%, 71.5% and 73.1%, respectively. Similarly, Xiao *et al.*

developed a new method for sleep staging based upon temporal and spectral analysis of HRV [88]. Their proposed method achieved sleep staging with high mean accuracy.

PTT has been suggested as a reliable marker for autonomic activation monitoring as well as the detection of sleep events. This study presents a new method for sleep stages classification. We analysed fingertip PPG and the ECG lead I to estimate spectral components of HRV and PTT in order to investigate whether these parameters can automatically detect sleep stages.

## 2.3.2 Methodology

**Subjects**: We analysed 20 subjects (11 females and 9 males with average age 45.6 $\pm$ 10.2 years) overnight PSG datasets collected at the Center for Sleep Medicine, Charite University Hospital (Berlin, Germany). Nine subjects were diagnosed with insomnia (6 females and 3 males) and 11 subjects were healthy (5 females and 6 males).

### 2.3.2.1 Data Acquisition and Preparation

Data had been recorded using a SOMNOscreen PSG system (SOMNOscreen PM, SOMNOmedics, USA). ECG and PPG data was included in PSG datasets and hypongrams were automatically scored by DOMINO sleep analysis software (DOMINO 2.6.0, SOMNOmedics, USA) and validated by a sleep technician independently of our research. The ECG signals had been recorded at a frequency sampling rate ($F_s$ ) of 256 Hz whilst $F_s$ for the PPG recordings was 128 Hz. Then ECG signals were firstly downsampled to $F_s$ = 128 Hz to match with PPG recordings. Sleep staging had been determined in the epoch with duration of 30 seconds. We divided each 30 seconds epoch into two sub-epochs with duration of 15 seconds. Similarly, PPG and ECG recordings were split up into 15 seconds segments (sub-epochs) in order to estimate PTT and HRV spectral features with higher accuracy and precision.

### 2.3.2.2 PTT Estimator

PTT is usually estimated through ECG and PPG analysis but in this study, we chose a different approach for PTT estimation. Since PPG signal represents blood flow and movement in the vessel, the first derivative of PPG could indicate the velocity of blood detected in the finger. Then the first derivative of PPG can be called velocity of PPG or VPG that can be calculated through Equation **1.1**. The time delay between the R wave in the ECG and the consecutive peak of VPG was assumed as PTT (Figure **2.10**). All biosignals were seg-

mented into sub-epochs with duration of 15 sec. The average PTT of each sub-epoch was appointed as its PTT feature.

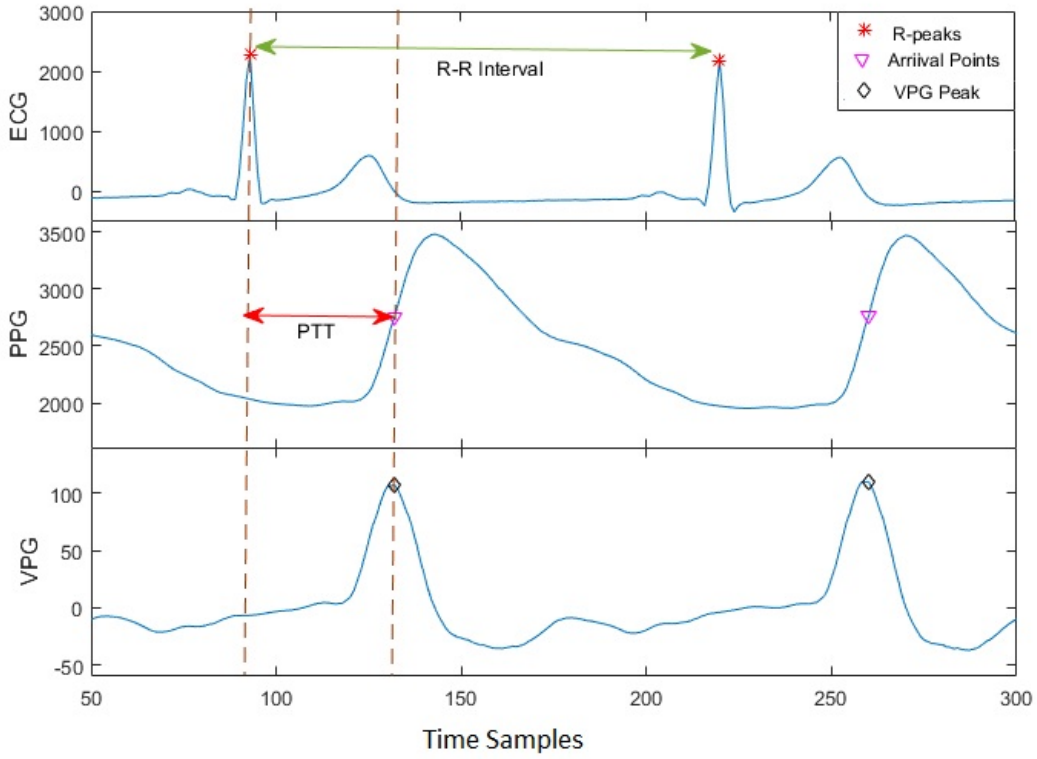



**Figure 2.12:** PTT estimation by using ECG and first derivative of PPG. PTT is pulse transit time from R wave to the consecutive peak of VPG.

### 2.3.2.3 HRV spectral analysis

HRV data was derived from beat-to-beat R-R interval. Once R waves of ECG were identified for each 15s segments, HRV was computed as the time delay between two consecutive R waves. The obtained HRV was resampled at 2 Hz and transformed to frequency domain using Welch's method [97]. The LF band power was defined as the percent power in the LF frequency band (0.05-0.15 Hz), and the HF band power was defined as the percent power in the HF band frequency (0.15-0.5 Hz) [115]. Both LF and HF data were normalised to their ranges. By this means, spectral power of HF and LF as HRV features were computed for every segment.

### 2.3.2.4 Development of Classifier

A classifier model was required to distinguish whether each 15 seconds sub-epoch belonged to NREM1, NREM2, NREM3 and REM sleep stages. The features matrix consisted of the

PTT, HF and LF band power of all sub-epochs in an overnight recording. Regarding to feature matrix, we developed linear classifiers including linear discriminant analysis (LDA) and linear SVM as well as non-linear classifier models like decision tree (DT), kNN and distance weighted k-NN (DW-kNN) for classification of sleep stages. LDA is a generalisation of logistic regression, however not limited to only two-class classification problem. SVM is a type of linear classifier that is capable to use to solve linear and non-linear problems. DT is non-linear method for classification of non-linearly separable data. The kNN is a non-parametric algorithm that seemed suitable for our classification purpose because it is not based on parameterised families of probability distribution. In addition, the kNN classifier was previously used for detection of sleep stages [132]. The distance weighted k-nearest neighbourhood (DW-kNN) algorithm is a refinement of k-NN classification method and assigns to weigh of contribution of the k-Neighbours according to their distance to the query point [137]. We developed our classifier models for sleep staging based upon these five classifiers. In each subject, either healthy or insomniac, developed classifiers identified sleep stages based on subject's features matrix. The performance of classifiers in detection of different sleep stages was evaluated and compared.

#### 2.3.2.5 Performance Analysis

To assess the performance of classifier model, we applied three statistical measures including sensitivity (Equation **2.5**), accuracy (Equation **2.7**) and positive predictive value (PPV) which can be calculated as following:

$$PPV = \frac{TP}{TP+FP} \times 100\%, \tag{2.8}$$

where true positive (TP) indicates the number of sub-epochs which their sleep stages was predicted correctly. false positive (FP) represent the number of epochs which their sleep stages was predicted incorrectly. In each subject, sensitivity refers to the fraction of a particular sleep stage which was classified accurately. While PPV represents the strength of the classifier in detection of a particular stage of sleep. Accuracy also indicates how generally was the performance of classifier in sleep staging.

### 2.3.3 Results and Discussion

Leave-one-out-cross-validation algorithm was used to assess the validation of our algorithm. Of the total 20 subjects in our dataset, features from 19 subjects were used for

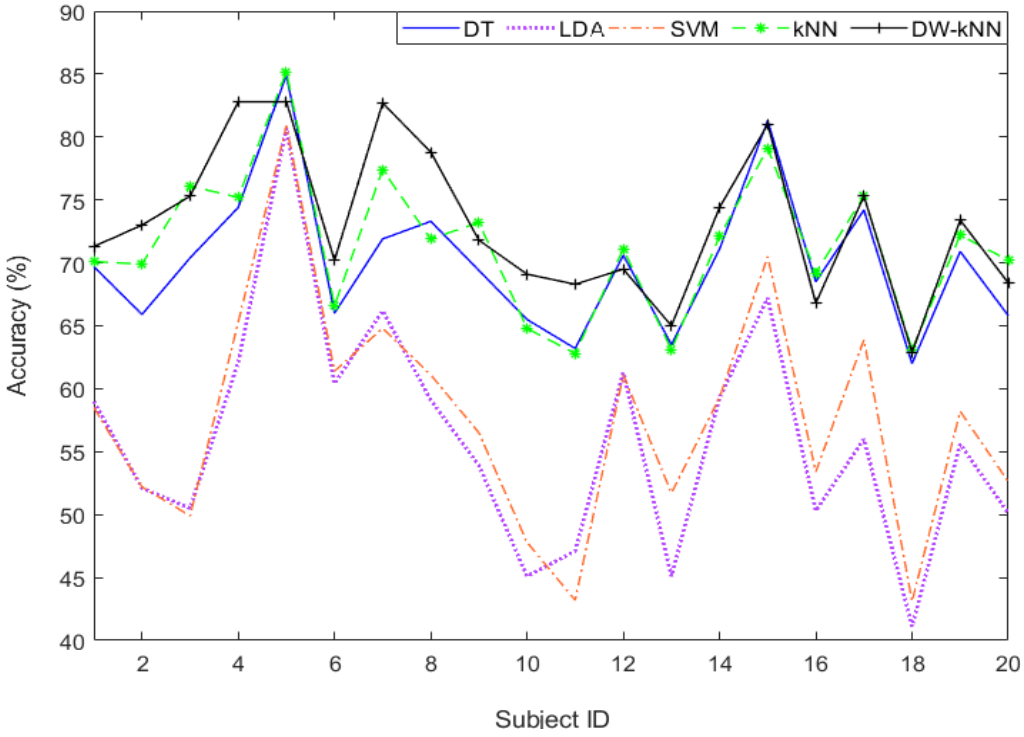



**Figure 2.13:** The comparison of accuracy of 5 classifiers in sleep staging. *DT*, *LDA*, *SVM*, *kNN* and *DW-kNN* refer to decision tree, linear discriminant analysis, support vector machine, k-nearest neighbourhood and distance weighted kNN classifier models, respectively.

training and data from the remaining one more subject used test. This process was being replicated for all 20 subjects and the overall sensitivity, PPV of each stage and accuracy of whole was computed. Figures **2.13** and **2.14** compared a the performance of various classifiers through accuracy, sensitivity and PPV. By this means, we could determine how various classifier performed in the detection of sleep stages.

Several PSG recordings such as EEG, eye movement and sub-mental EEG are normally required to provide an accurate sleep staging detection. In this study, we focused on ECG and PPG biosignals as two measures of cardiovascular functions, for automatic detection of sleep stages. PTT has been known as a reliable and non-invasive measure for widespread applications from continuous measurement of blood pressure to the sleep events detection e.g apneic episodes or micro-arousals [51, 111, 125]. Since PTT is a marker of autonomic function, we hypothesised it can take an effective role in the determination of sleep stages.

We visualised the obtained results in order to compare the performance of linear and

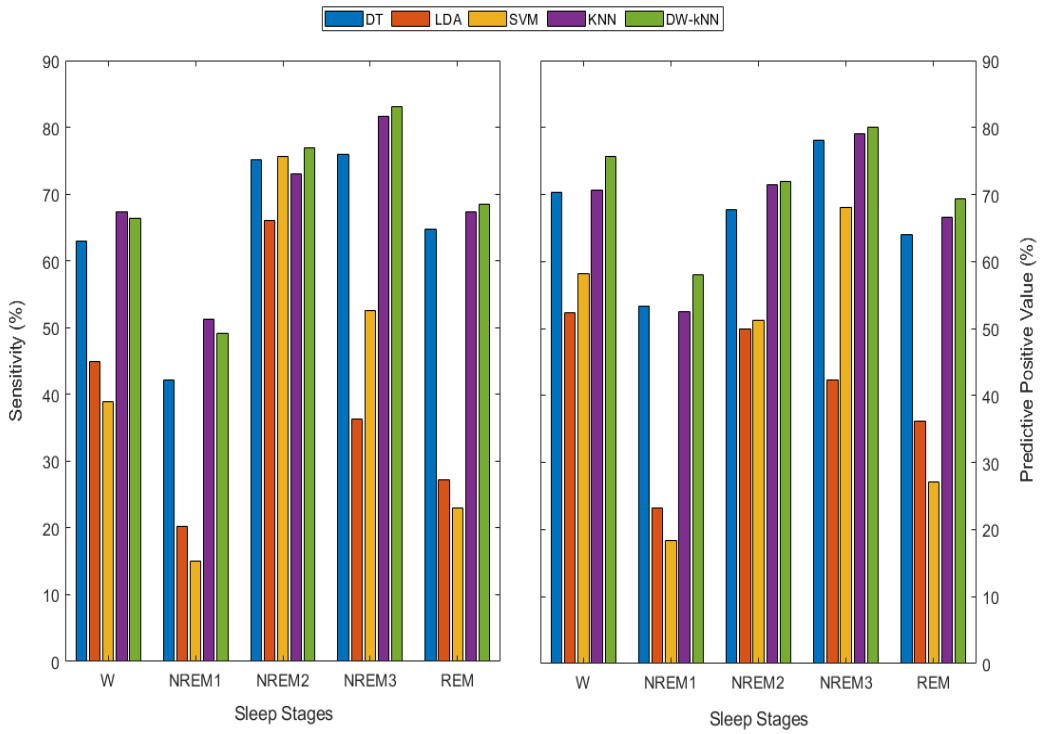



**Figure 2.14:** The comparison of sensitivity and predictive positive value of classifier models in sleep staging.

non-linear classifiers in detection of different sleep stages as well as in different patients group. Non-linear classifier models reached a higher accuracy than linear models almost in all subjects (Figure **2.13**). The average accuracy in all non-linear classifiers was greater than 70% ($Accuracy_{DT} = 70.1\%$, $Accuracy_{kNN} = 71.4\%$ and $Accuracy_{DW-kNN} = 73.4\%$, ), whilst in linear models, it was less than 60% ($Accuracy_{LDA} = 56.1\%$ and $Accuracy_{SVM} = 57.8\%$). Particularly, DW-kNN model had the most successful performance in sleep staging where the accuracy in only one subject was below of 65%, whilst it reached over 80% in 4 subjects. As shown in Figure **2.14-Left**, the sensitivity of non-linear models in detection of REM, NREM1 and NREM3 sub-epochs were comparably greater than linear models. The linear SVM classifier could accurately detect stage 2 sub-epochs with average sensitivity of about 75%, whilst its sensitivity was below 55% in detection of other sleep stages. PPV analysis also shows that non-linear classifiers could detect all stages with higher PPV (Figure 2.14-Right). A visual comparison of the performance of all classifier models in 20 subjects demonstrates that DW-kNN classifier could detect sleep stages with higher accuracy and greater sensitivity and PPV. In insomniac subjects group, non-linear classifiers like DT, kNN and could launch sleep staging with average accuracy of 70.3% and 71.6%, re-

| Subject ID | Conditions | Wake | | NREM1 | | NREM2 | | NREM3 | | REM | | Accuracy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | SEN(%) | PPV(%) | SEN(%) | PPV(%) | SEN(%) | PPV(%) | SEN(%) | PPV(%) | SEN(%) | PPV(%) | (%) |
| 1 | I | 35 | 63 | 43 | 55 | 81 | 66 | 86 | 90 | 73 | 73 | 71.3 |
| 2 | H | 70 | 70 | 46 | 48 | 80 | 73 | 63 | 67 | 63 | 59 | 73.0 |
| 3 | H | 54 | 65 | 56 | 64 | 79 | 72 | 88 | 87 | 85 | 84 | 75.3 |
| 4 | I | 84 | 85 | 59 | 53 | 82 | 77 | 88 | 91 | 60 | 71 | 82.8 |
| 5 | H | 94 | 94 | 59 | 68 | 71 | 66 | 82 | 76 | 74 | 74 | 82.8 |
| 6 | H | 76 | 77 | 43 | 46 | 73 | 66 | 66 | 66 | 80 | 81 | 70.2 |
| 7 | I | 79 | 82 | 61 | 70 | 83 | 77 | 95 | 91 | 75 | 74 | 82.7 |
| 8 | I | 68 | 81 | 74 | 58 | 82 | 75 | 90 | 92 | 64 | 59 | 78.8 |
| 9 | I | 64 | 84 | 44 | 60 | 89 | 65 | 86 | 87 | 69 | 68 | 71.8 |
| 10 | H | 55 | 69 | 49 | 58 | 77 | 68 | 84 | 81 | 59 | 62 | 69.1 |
| 11 | I | 55 | 69 | 55 | 66 | 77 | 68 | 74 | 71 | 66 | 66 | 68.3 |
| 12 | H | 36 | 75 | 43 | 73 | 90 | 64 | 82 | 86 | 22 | 60 | 69.5 |
| 13 | H | 49 | 68 | 43 | 58 | 84 | 55 | 84 | 84 | 23 | 56 | 65.0 |
| 14 | I | 36 | 60 | 49 | 59 | 87 | 71 | 76 | 82 | 58 | 78 | 74.4 |
| 15 | H | 92 | 87 | 59 | 61 | 53 | 55 | 76 | 57 | 70 | 68 | 81.0 |
| 16 | I | 38 | 70 | 55 | 56 | 82 | 59 | 90 | 91 | 47 | 61 | 66.8 |
| 17 | H | 72 | 81 | 86 | 71 | 66 | 68 | 89 | 82 | 81 | 94 | 75.3 |
| 18 | H | 71 | 75 | 39 | 43 | 72 | 59 | 68 | 64 | 72 | 68 | 62.9 |
| 19 | I | 57 | 78 | 36 | 53 | 87 | 75 | 73 | 72 | 81 | 79 | 73.4 |
| 20 | H | 60 | 76 | 58 | 57 | 63 | 61 | 85 | 78 | 57 | 62 | 68.4 |
| Mean | - | 61.9 | 74.7 | 53.1 | 77.7 | 80.7 | 67.0 | 81.3 | 79.8 | 64.0 | 69.9 | 73.4 |
| Std | - | 18.3 | 10.0 | 12.1 | 8.2 | 9.4 | 6.8 | 8.8 | 10.5 | 17.1 | 9.9 | 6.4 |

**Table 2.5:** Performance of the DW-kNN classifier model in sleep staging by using Leave-one-out-cross-validation method. **Sen** and **PPV** indicate respectively sensitivity and positive predictive values. **H** and **I** represent diagnosed healthy and insomnia subject, respectively.

spectively. The performance of linear classifiers in sleep staging of insomniac subject were significantly weaker ($Accuracy_{LDA} = 56.9\%$ and $Accuracy_{SVM} = 57.8\%$). In healthy group, the average accuracy of 55.4%, 57.7%, 70%, 71.3% were obtained for LDA, SVM, DT, kNN and classifiers, respectively.

The detailed results of detection of sleep stages using DW-kNN classifier in two group of healthy and insomniac subjects are presented in Table **2.5**. The mean accuracy of patients with Insomnia was 74.5%, nonetheless, it reached to about 72% in healthy subjects. The average accuracy of both groups were very close and it therefore proved that the performance of algorithm was completely independent of subjects' sleep conditions (Figure **2.15**).

As shown in Figure **2.16**, the average sensitivity for the differentiation of wake sub-

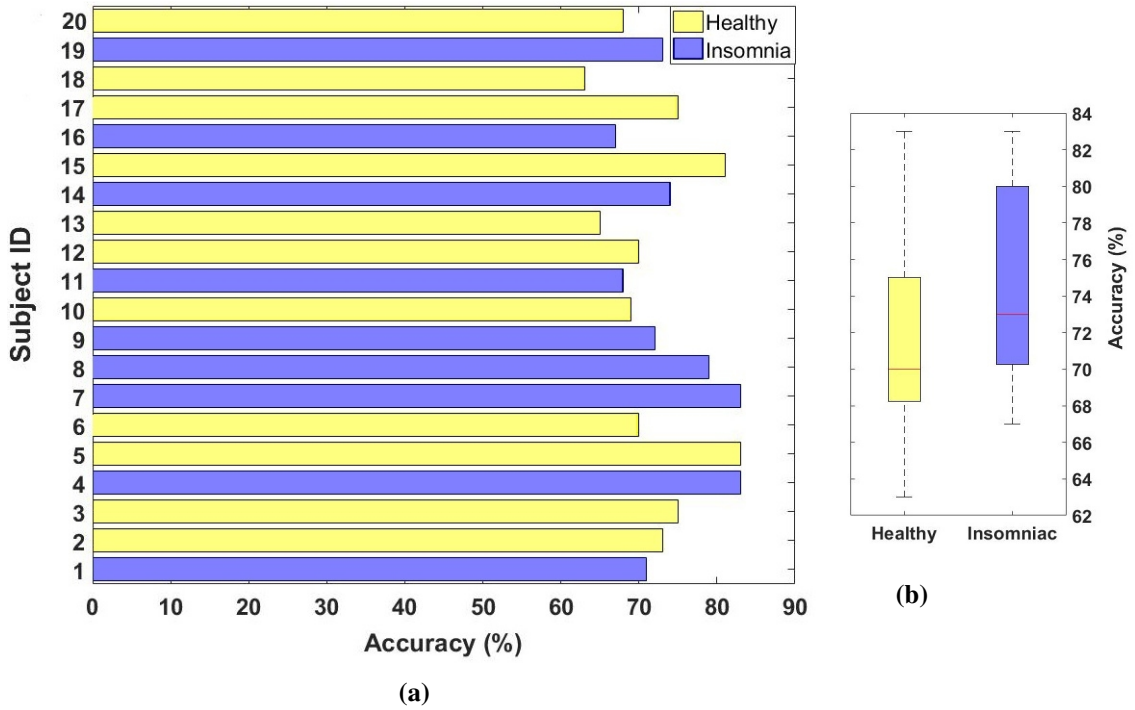
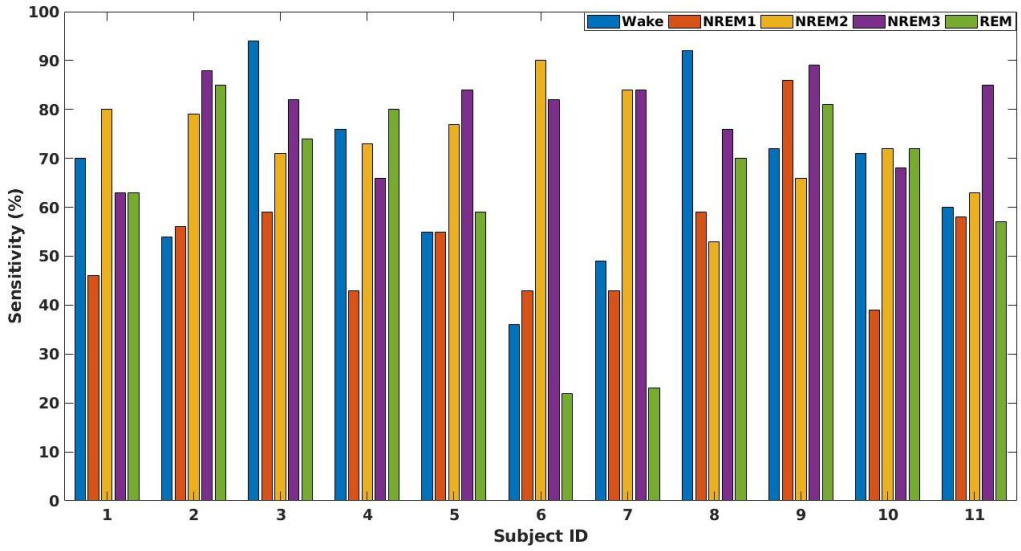


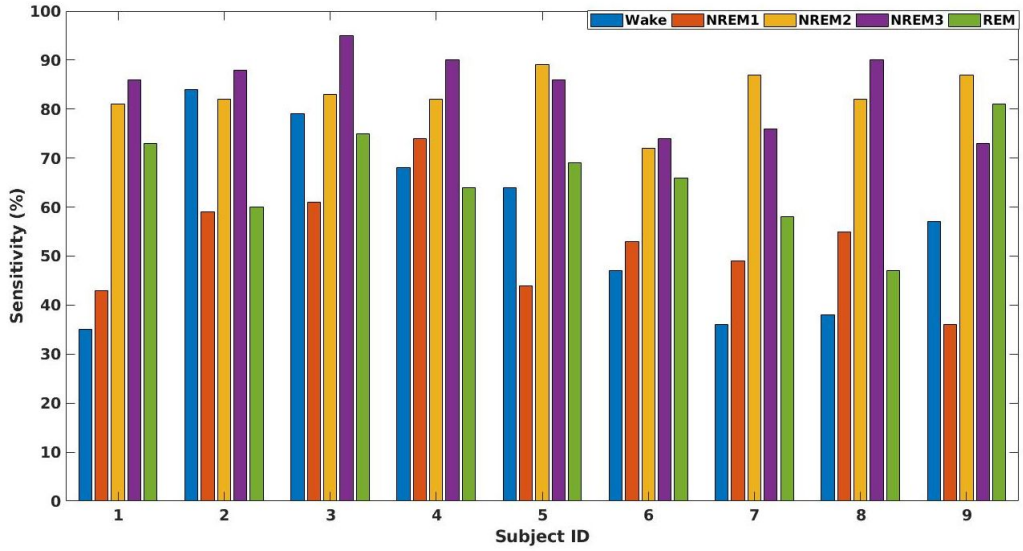

**Figure 2.15:** A graphical comparison of obtained accuracy of DW-kNN classifier in detection of sleep stages in healthy and insomniac subjects.

epochs from sleep epochs was 61.9%. Similarly, the algorithm could identify sub-epochs with NREM sleep stage 1, 2 and 3 with an average sensitivity of 53.1%, 80.7% and 81.3%, correspondingly. Whilst the mean sensitivity of algorithm for REM sub-epochs was about 64%. Our algorithm was more powerful in stages 2 and 3 of NREM with an average sensitivity of over 80%. The average PPV for the detection of wake sub-epochs was 73.5% whilst it was 77.2%, 67.0%, 79.8% and 69.9% for classification of NREM1, NREM2, NREM3, and REM respectively. We compared the average sensitivity of algorithm in detection of each sleep stage in both healthy and insomniac groups and found that the algorithm was able to classify NREM1 sub-epochs in healthy subjects with average sensitivity of 0.7% greater than insomnia patients. On the contrary, the algorithm was more sensitive to identify NREM2, NREM3 and REM sub-epochs in patients with insomnia than healthy subjects where the average sensitivity was greater by 9.3%, 5.4% and 3.5%, respectively. The proportion of waking sub-epochs in patients with insomnia should be more than healthy subjects. Thus, we expected the higher number waking epochs would affect the accuracy of algorithm and consequently overestimated the number of detected waking epochs in insomniac patients. However, we observed the mean sensitivity of detected waking epoch in

healthy group was overwhelmingly greater than insomniac group by 9.9%. Therefore, the performance of proposed technique was not associated to sleep latency.




**(a)**




**(b)**

**Figure 2.16:** The sensitivity of DW-kNN based algorithm in detection of sleep stages. (**a**) healthy subjects and (**b**) patients with insomnia

Researchers suggested methods for sleep staging based on HRV analysis [88, 136], however this research has suggested applying the PTT alongside with HRV spectral components for sleep staging. Since PTT like HRV can be used for monitoring of autonomic system function, it is imperative to investigate whether PTT could predict sleep stages. In a similar research, the capability of model based on PPG pulse rate variability and combined

with HRV for detection of sleep stages in children were evaluated [138]. Their developed SVM classifier model could detect REM and NREM stages with accuracy of 77%. Then, for future studies PTT and HRV models can be assessed in children subjects for sleep staging.

### 2.3.4 Conclusion

This study presented a new developed algorithm for sleep staging by using a combination of PTT and HRV extracted features. The DW-kNN classifier based-algorithm could detect sleep stages with average accuracy of 73.4% when the lowest accuracy was about 63%. This manifests that the classification model performed successfully. We also evaluated classifiers in two groups (healthy and insomnia patients) and we achieved similar results in both cases. This indicates that our recommended method can distinguish sleep stages either subjects was healthy or suffered from insomnia. Development of the algorithm was completely independent of EEG, sub-mental EMG and eye movement recordings and their considerable number of electrodes and sensors. It means that our suggested method requires fewer recordings and subsequently fewer electrodes. Furthermore, wearable technologies have recently become considerably popular for screening purposes, as a consequence a sleep staging technique which is not very complicated and does not require a bunch of sensors and electrodes could be highly desirable. For improving the performance and reaching higher accuracy in sleep staging, further spectral and temporal HRV features along with PTT biomarker can be evaluated. The algorithm can be implemented and used as a simple, reliable and wearable instrument for home-based sleep screening. Further studies with wider range of subjects with different sleep disorders are required to assess the algorithm performance in different conditions

# Chapter 3

# Overnight Continuous BP Estimation

## 3.1 Background

Development of a reliable and non-invasive method for continuous BP estimation is challenging. Since all cuff-based methods require pauses during measurement, they will miss some points of measurement and they would not be able to measure BP without any interruptions. Pulse transit time as a marker of autonomic activity has been recommended as a reliable alternative for continuous BP estimation (CBPE) [44, 51, 53, 139]. PTT can be used either directly or indirectly for development of CBPE models. Ye *et al.* estimated PTT from ECG and fingertip PPG and then tried to develop an empirical equation for CBPE [44]. Another study suggested a method for non-invasive and continuous BP measurement, based on pulse wave velocity (PWV) derived from PTT analysis [51]. PWV is defined as the speed of propagation of a BP pulse and dependant to the number of arterial properties such as elasticity, thickness, diameter and the density of the blood [140]. PWV is also reversely associated with PTT [51]. In addition, due to some similarities in PPG and arterial BP waveform morphology [139], features extracted from PPG can therefore be effective in BP estimation. Thus, PPG characteristics and derivations have been utilised for CBPE in few studies [141, 142]. Li and his team extracted about 20 features from PPG and applied them alongside with PTT to develop a reliable CBPE model. PPG-based CBPE model resulted a significant underestimation (8 mmHg) in SBP measurement and considerable overestimation (10 mmHg) in compare with cuff pressure. Nevertheless, a combination of PTT time spans and PPG morphology characteristics could improve BP estimation [141]. In another research, 14 features from second derivative of PPG (APG) were extracted and applied along with PPG features to estimate BP [142]. Their findings demonstrated that a

combined model of PPG and APG could improve BP measurement by 40%.

In this chapter, first and second derivatives of PPG (VPG and APG) were extracted through PPG analysis to estimate $PTT_v$ and $PTT_a$ and then to develop PTT-BP models for continuous BP estimation. We compared results of both $PTT_v$ and $PTT_a$- based models with existing BP reference values to find out which model provided more accurate SBP and DBP measurements.

## 3.2 Methodology

### 3.2.1 Data Acquisition

We utilised PSG data of 6 female and 4 male subjects with the average age of 45.8 $\pm$ 11.2 collected in the Center for Sleep Medicine, Charite University Hospital (Berlin, Germany). Six subjects suffered from insomnia (2 males and 4 females) whilst four subjects were healthy (2 males and 2 females). PSG Data was recorded using SOMNOscreen PSG system (SOMNOscreen PM, SOMNOmedics, USA) which provided 33-channel recordings. We utilised only ECG, PPG and BP data. The ECG had been recorded at a sampling rate ($F_s$) of 256 Hz whilst PPG was recorded at 128 Hz. Existing arterial systolic and diastolic reference blood pressure ($SBP_r$ and $DBP_r$) data were automatically measured using analysis software, DOMINO 2.7 (DOMINO, SOMNOmedics, USA) at $F_s$ = 4 Hz. Arterial BP values were then be calibrated with the Riva Rocci sphygmomanometer method before and during the recording. These existing blood pressure values were called reference systolic and diastolic blood pressures ($SBP_r$ and $DBP_r$) and were later used to validate our empirical techniques.

### 3.2.2 Data Preparation

Data from three subjects were used to develop BP-PTT models (pilot group) and data from seven more subjects were considered as control group and being employed to validate obtained models. Subjects were randomly selected for pilot and control groups. ECG signals firstly were down-sampled to $F_s$ of PPG (128 Hz) to match with PPG by averaging. ECG and PPG recordings were segmented into sub-segments with duration (d) of 3 seconds. $SBP_r$ and $DBP_r$ data were divided into 3 seconds segments and the mean value of each segment was calculated and considered for further analysis. By this means, we could measure blood pressure and validate by $SBP_r$ and $DBP_r$ every 3 secs.

### 3.2.3 PPG Derivatives and PTT Estimation

The first and second derivatives of PPG (VPG and APG) are known as two interpretations of PPG characteristics [143]. The PPG signal is filtered with low- and high-pas FIR filters to eliminate DC components and high frequency noise with cutoff frequencies of 30 Hz and 0.5 Hz, respectively. Both filters are designed using the window method, with the Hamming window function where the corresponding filter orders are chosen as 500 for the low-pass after and 4000 for the high-pass filter [144].

Both VPG and APG signals were obtained using a 3-point numerical differentiation derivative function. To minimise noise effect during computation of VPG and APG, band-pass and moving average filters were applied to smooth the signal after derivation. We employed critical points of VPG and APG for estimation of PTT. After detection of R-waves [101], we used them as the first arterial points for PTT estimation. The second arterial site is where the pumped blood reaches and is tracked by fingertip sensor and is called pulse pressure arrival point. Different points have been considered by different devices as arrival points such as points whose amplitude values are 50% or 25% of PPG pulse amplitude and located exactly after R-wave peaks [111, 112]. Here, peaks of VPG and APG were considered as two different arrival points. The VPG peak indicates when pulse wave reaches the highest velocity whilst APG peaks or a-waves represents systolic positive point. As a consequence, two different types of pulse transit time were obtained including $PTT_V$ , $PTT_A$ which indicate respectively the time difference from R-wave to the consecutive VPG and APG peak points (Figure **3.1**).

### 3.2.4 PTT and Estimation of Overnight Blood Pressure

Our aim was to formulate models to find out the relationships between different types of PTT and blood pressure, then to determine which type of computed PTT can accurately estimate systolic and diastolic blood pressures. Hence, for the development of empirical functions, three subjects' two types of PTT ($PTT_A$ and $PTT_V$ ) alongside with $SBP_r$ and $DBP_r$ time series were used to develop the optimal fitting curve. We created two models of PTT-BP, where the first model was called **Model A** and developed to fit $PTT_A$ and $SBP_r$ and $DBP_r$ values. Another model was **Model V** and was created to fit $PTT_V$ and $SBP_r$ and $DBP_r$ time series. In case of SBP measurement, two functions were empirically estimated by using polynomial curve fitting. Figure **3.2** shows how we used curve fitting to model $PTT_A - SBP$ and $PTT_V - SBP$ relations by employing second-degree polynomial. Eventually, two

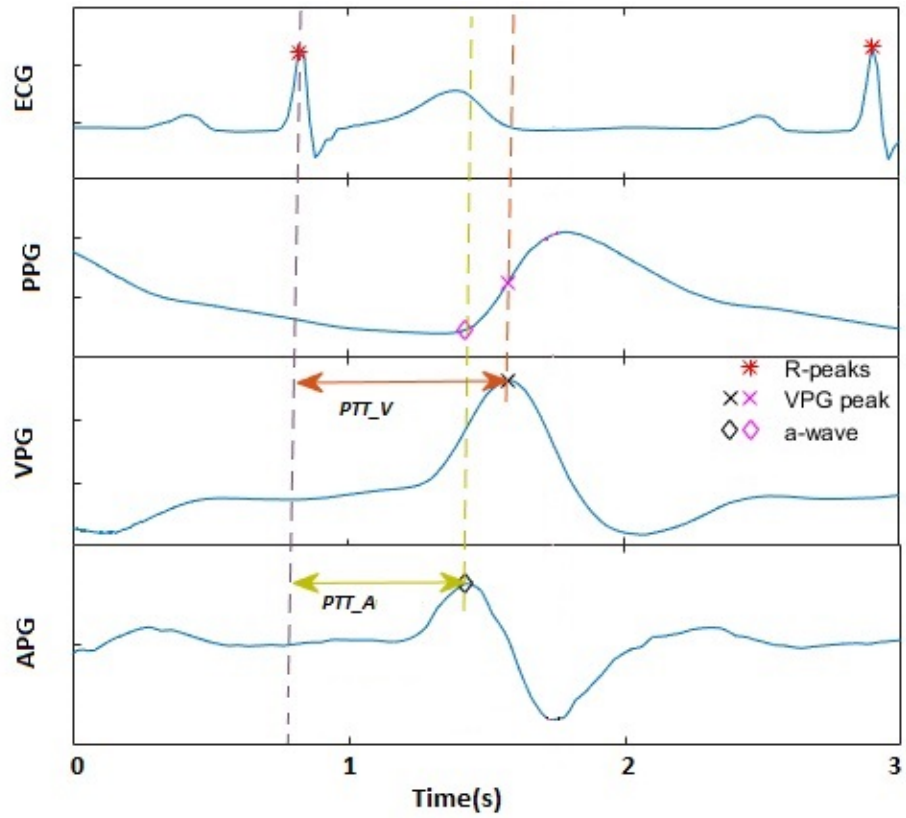



**Figure 3.1:** Two techniques for PTT detection. $PTT_V$ is pulse transit time from ECG **R** wave to the VPG peak. $PTT_A$ represents pulse transit time from ECG **R** wave to *a-wave*.

following functions were constructed to fit systolic blood pressure and different types of PTT ($PTT_A$ and $PTT_V$) in order to predict SBP through PTTs:

$$SBP_A = 0.0029 \times (PTT_A)^2 - 1.958 \times PTT_A + 414.9, \tag{3.1}$$

$$SBP_V = -0.0028 \times (PTT_V)^2 + 1.091 \times PTT_V + 28.72. \tag{3.2}$$

Curve fitting process were replicated in to fit different types of pulse transit time ($PTT_A$ and $PTT_V$) and diastolic blood pressure. Equations **3.3** and **3.4** were also empirically created to realise $DBP_A - DBP$ and $DBP_V - DBP$ relationships.

$$DBP_A = -0.0024 \times (PTT_A)^2 + 1.77 \times PTT_A - 212.9, \tag{3.3}$$

$$DBP_V = -0.0007 \times (PTT_V)^2 + 0.1342 \times PTT_V + 87.39. \tag{3.4}$$

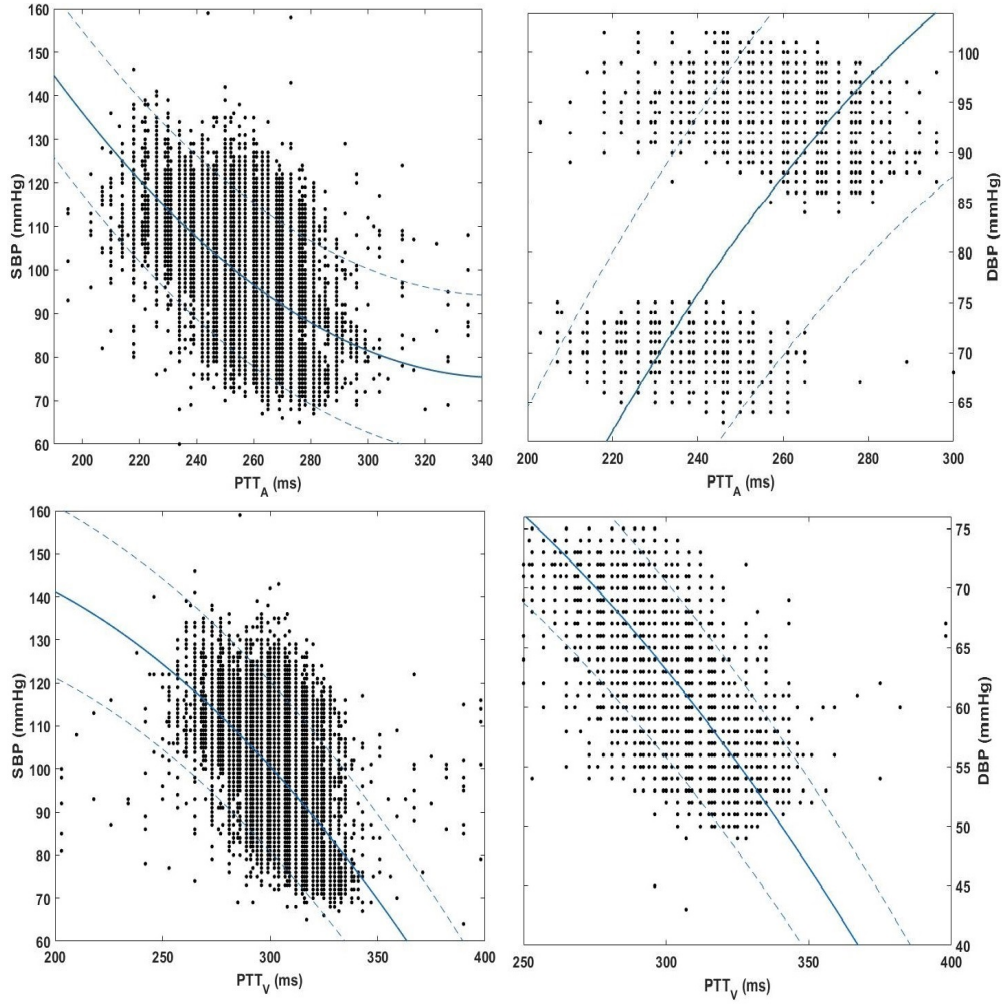



**Figure 3.2:** The empiric PTT-BP functions. **(Top)** Schematic of **Model A** fitting curve: (Right) $SBP - PTT_A$, Left: $DBP - PTT_A$. **(Bottom)** Schematic of **Model V** fitting curve: Right: $SBP - PTT_V$, (Left) $DBP - PTT_V$. The confidence intervals of 95% was indicated by dashed-lines in all diagrams.

## 3.3 Performance Analysis

After development of curve fitting models, it is necessary to evaluate how each model can estimate SBP and DBP. To assess the performance of either model A or V, we referred to seven subjects in the control group. Their $PTT_A$ and $PTT_V$ were computed and then used to evaluate functions of models A and V. We finally compared resulted SBP and DBP of both models to the reference values ($SBP_r$ and $DBP_r$) using goodness of fit analysis and Bland-Altman plots. Two goodness of fit parameters including $R^2$ and root mean square error (RMSE) were calculated. $R^2$ represents the square of the correlation between response

and predicted values whereas RMSE computes the mean error of the approximation. Bland-Altman plots were also applied to compare results of two methods with reference BP values.

## 3.4 Results

The outcomes of goodness of fit analysis were tabulated in Table **3.1** and **3.2**. indicate which PTT-BP model estimated overnight continuous SBP and DBP more accurately. In case of systolic blood pressure measurement, model V was more precise with the average $R^2$ of 0.593 and the mean error of $\pm$3.96 mm-Hg with standard deviation of 1.41 were achieved. Whilst the average $R^2$ in Model A was 0.488 and mean error reached to $\pm$9.23 mm-Hg which was considerably higher than Model V.

| Subject | Model A | | Model V | |
|---|---|---|---|---|
| ID | $R^2$ | RMSE | $R^2$ | RMSE |
| 1 | 0.338 | 4.08 | 0.467 | 4.32 |
| 2 | 0.526 | 7.00 | 0.715 | 1.36 |
| 3 | 0.828 | 11.13 | 0.791 | 2.85 |
| 4 | 0.289 | 12.91 | 0.393 | 5.54 |
| 5 | 0.65 | 10.19 | 0.664 | 4.26 |
| 6 | 0.097 | 8.48 | 0.383 | 4.88 |
| 7 | 0.691 | 10.83 | 0.741 | 4.53 |
| Mean | 0.488 | 9.23 | 0.593 | 3.96 |
| SD | 0.258 | 2.96 | 0.174 | 1.41 |

**Table 3.1:** Statistical analysis of two recommended models for estimation of systolic blood pressure. *Mean* and *SD* indicate the average and standard deviation value of $R^2$ and RMSE for each model.

Figure **3.3-a** shows Bland-Altman plot for SBP estimation of Model A that compares the estimated SBP values from model A ($SBP_A$) with reference values ($SBP_r$). The agreement limits were $mean_{SBP_A,SBP_r} \pm$ 34.4 mmHg where about 4% of [$SBP_A$ $SBP_r$] pairs were located beyond the limits. Similarly, the agreement limits for model V were $mean_{SBP_V,SBP_r} \pm$ 28.8 mmHg where 3.2% of [$SBP_V$ $SBP_r$] were located beyond the limits (Figure **3.3-b**). As shown, the difference between $SBP_V$ and $SBP_r$ was 6 mmHg smaller than difference between $SBP_A$ and reference values. In addition, the greater percentage of SBP data in Model

| Subject | Model A | | Model V | |
|---|---|---|---|---|
| ID | $R^2$ | RMSE | $R^2$ | RMSE |
| 1 | 0.219 | 6.49 | 0.321 | 6.01 |
| 2 | 0.362 | 2.95 | 0.393 | 1.68 |
| 3 | 0.739 | 8.92 | 0.722 | 9.48 |
| 4 | 0.250 | 6.16 | 0.181 | 9.91 |
| 5 | 0.551 | 10.59 | 0.559 | 4.27 |
| 6 | 0.015 | 8.98 | 0.245 | 8.49 |
| 7 | 0.484 | 6.85 | 0.494 | 8.35 |
| Mean | 0.374 | 7.28 | 0.416 | 6.88 |
| SD | 0.240 | 2.49 | 0.189 | 3.03 |

**Table 3.2:** Statistical analysis of PTT-DBP models

A were outside of the agreement limits in compare to Model V by 0.7%. Goodness of fit parameters and BA plots both indicate that Model V had stronger and more precise SBP estimation than Model V.

Likewise, Model V had better results in DBP estimation whilst its average $R^2$ was higher by almost 4% greater than Model A. Albeit, the difference of two mean errors in diastolic blood pressure measurement was negligible (Table **3.2**). Bland-Altman plots of DBP estimation shows that the difference between $DBP_A$ and $DBP_V$ with $DBP_r$ were about 52 and 21 mmHg, respectively. Moreover, only 1.5% of estimated DBP through Model V ($DBP_V$) were beyond the agreement limits, whilst this rate for Model A ($DBP_A$) was more than twice (3.5%) (Figure **3.4**). This means that model V could also estimate DBP more precisely than model A.

## 3.5 Discussion

In this chapter, we presented our empirical models for overnight continuous BP monitoring by using PTT which was extracted from ECG and derivatives of PPG. PTT has been used in development of a cuff-less surrogate technique for BP estimation in several studies [44, 51, 53, 140, 145, 146]. A key point in PTT detection is the arrival time of the pulse wave in the periphery (finger), though there in no agreement about that in literature. Several

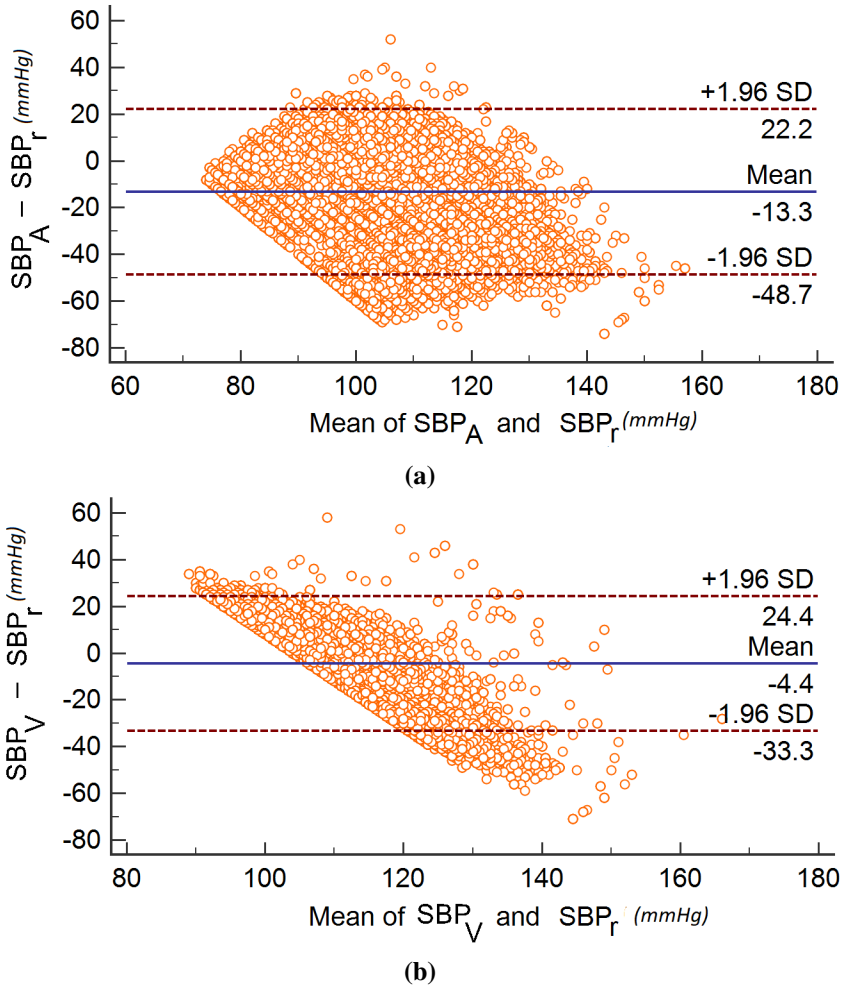



**Figure 3.3:** Bland-Altman plots of the continuous SBP data of 7 subjects. Each point represents SBP for 3 secs. (**a**) Estimated SBP through Model A ($SBP_A$) where 3.9% of all pairs are located beyond the agreement limits (mean $\pm$ 1.96 SD). (**b**) Estimated SBP through Model V ($SBP_V$) where 3.2% of all pairs are located beyond the agreement limits. $SBP_r$ represents reference values of systolic BP.

studies considered the peak of PPG as arrival point [140, 53] while 25%, 50% or 60% of PPG pulse amplitude was assigned as arrival point for PTT estimation in other researches [44, 51, 146]. However, our empirical models estimate PTT through haemodynamic features such as the velocity and acceleration of blood in vessels. $PTT_V$ provided a more consistent and accurate measure than $PTT_A$ to estimate blood pressure. In other words, if the VPG has been used for detection of PTT, the obtained PTT ($PTT_V$) could produce more precise and accurate results than PTT detected by second derivative of PPG. In fact, the peak of VPG waveform represents when the blood flow which is pumped from left ventricle reaches the maximum velocity in peripheral circulation. Here we presented a technique for

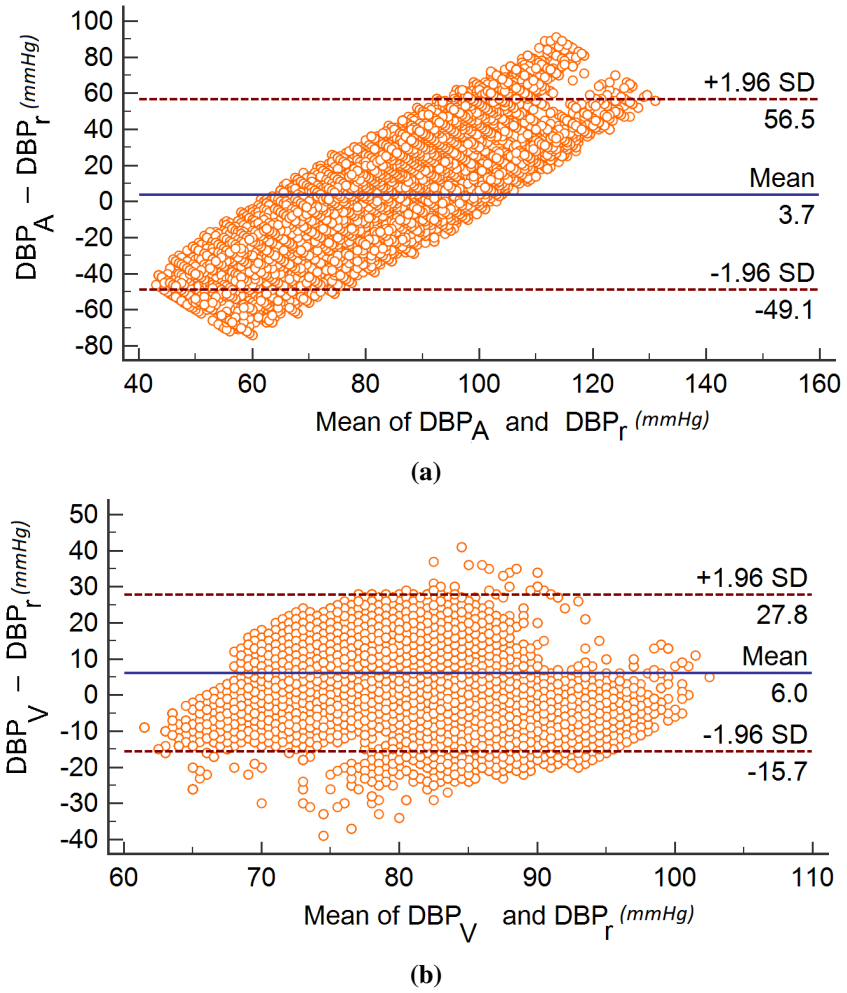



**Figure 3.4:** Bland-Altman plots of the continuous DBP data of 7 subjects. (**a**) Estimated DBP through Model A ($DBP_A$) where 3.5% of all pairs are located beyond the agreement limits (mean $\pm$ 1.96 SD). (**b**) Estimated DBP through Model V ($DBP_V$) where 1.5% of all pairs are located beyond the agreement limits. $DBP_r$ represents reference values of diastolic BP.

BP estimation directly from PTT-SBP/DBP curve fitting models. However, PTT has been mainly utilised to compute pulse wave amplitude and then indirect estimation of BP. PWV by definition represents the velocity of blood propagation and it seems to be closely related with VPG. The significant difference between PWV-BP based models and our developed PTT-BP model is in the various techniques which were applied for estimation of the BP velocity. Both PWV and VPG can describe the velocity of BP pulse, however PWV estimation, firstly, requires PTT detection, while VPG can be directly obtained from PPG analysis and its peak can be used for PTT estimation. Indeed our method was independent of PPG pulse amplitude and was associated to the morphology of PPG first derivative. For devel-

opment PTT-BP models, ECG and PPG recordings of PSG database were used. Thus, for each subject, averagely 6 hours and 50 minutes continuous BP were estimated and validated through reference values every 3 secs. The BP estimator models have often been developed from shorter duration data (15 or 30 minutes) [53, 147] or 90 minutes [140], however in this study, we developed models using considerably longer duration datasets and evaluated with at least 6 hours extracted PTT and BP reference values. The goodness of fit parameters for both SBP and DBP analysis show that model V could estimate continuous BP with higher accuracy than model A even in several hours recording. Thus, VPG seems to be more effective than APG for continuous BP monitoring.

On the other hand, 1.96 SD for both DBP and SBP measurement in model A and V are debatable in terms of whether developed models are usable or not. The agreement limits of model V for continuous SBP and DBP estimation was considerably smaller than model A. This manifests the more accurate performance of model V in contrast to model A. However the obtained 1.96 SD for model V were 29 and 21 mmHg for SBP and DBP, respectively. This contradicts the high capability of model V in accurate continuous BP estimation as we expected. This reflects PTT limitations in BP estimation, specifically during the sleep. In this study, we evaluated two method for PTT estimation, however, we did not consider the effect of pre-ejection period (PEP), which is the time between the onset of electrical cardiac activity and the start of mechanical ventricular ejection. PEP contributes significantly to the PTT [51] and is accounted as a cause of PTT variability [148].

PPG signal differentiation may generate destructive noise which affect on the detection of critical points of VPG and APG. In other words, a simple differentiator works as a high-pass filter and could amplify the high frequencies like unwanted noises, correspondingly. Our approach was to use smoothing and averaging window filters after differentiation. Another suggested technique is using Smooth Noise Robust Differentiator (SNRD) which is precise at low frequencies, smooth and guaranteed suppression of high frequencies [144].

In this study, the limited number of subjects were applied for development of models ($n = 3$) and test of models ($n = 7$). More subjects either men or women with different age and medical condition will allow to gain a comprehensive comparison of APG and VPG features in continuous BP monitoring as well as to develop robust and more precise BP estimators. The effect of random selection in BP estimation can also be determined in future studies with larger sample size.

## 3.6 Conclusion

This study shows that $PTT_V$ as time delay between from ECG and the first derivative of PPG peaks is correlated with both systolic and diastolic blood pressure. The empirical quadratic polynomials could model PTT-SBP and PTT-DBP relations and resulted models could estimate overnight SBP and DBP. This research illustrated that derivatives of PPG, particularly, VPG can also be considered as a non-invasive measure for haemodynamic monitoring. The obtained algorithm is capable to be improved and utilised for real-time and overnight blood pressure monitoring.

# Chapter 4

# Arousals and ECG Time Intervals

## 4.1 Background

Heart rate is a vital measure of cardiovascular function and can be measured from R-R time intervals. Heart rate variability has been analysed in various studies in order to monitor sleep events and diagnosis of sleep disorders [71, 72, 83, 149]. In chapter 2, HRV frequency components were extracted and applied to develop an algorithm for sleep staging as well as to investigate whether different types of sleep arousals influence on low and high frequency spectral components of HRV. Despite of diagnostic significance of HR in sleep studies, it is not the only cardiovascular marker which can be extracted from ECG. In addition, HR does not seem as a robust index of potentially pro-arrhythmic changes that may occur in the cardiac conduction system in the atrial or ventricular myocardium [91]. The QT interval reflects subtle temporal variations in ventricular depolarisation and repolarisation and also exhibit spontaneous beat-to-beat fluctuations [150]. QT interval can be affected in patients suffering from obstructive sleep apnoea (OSA). Specially, the variance of beat to beat QT interval are correlated with the severity of obstructive sleep apnoea [94]. This correlation is even stronger than standard measures of HRV.

The main objective of this chapter was to evaluate whether sleep arousals can cause a significant change in cardiac QT and RR time intervals. In addition, this study was going to study and compare the instantaneous changes of cardiac intervals pre- and post-arousal. The variability of both QT and RR before and after arousal onset was also investigated. Since different sleep events such as respiratory or limb movement episodes may induce transient arousals, we also compared QT/RR interval changes during occurrence of different types of arousals to explore the association of sleep events and QT/RR intervals fluctuations. The

effect of sleep stage and duration of the arousal episode on QT and RR interval variability were also studied.

## 4.2 Methodology

### 4.2.1 Data Acquisition

The MrOs Sleep Study is a multi-centre cohort study which was conducted between December 2003 and March 2005 with more than 3135 community-dwelling men, 65 years old or older participants at 6 different clinical centres in the United States. All men provided written informed consent, and the study was approved by the Institutional Review Board at each site. All men completed in-home overnight polysomnography, however we had access to 2892 subjects' PSG datasets. The participants' PSG data was recorded over one night at their residence using the Sleep Monitoring System (Safiro, Compumedics, Inc, Chatlotte, NC, USA). Since our goal was to focus on sleep arousals and cardiac time intervals, we only considered subjects whose PSG recordings was fairly adequate and their sleep had a proper number of arousals. Finally PSG dataset of 2659 (91.9%) were utilised and analysed in this study.

Each dataset contained 22 channels. We only analysed one central EEG channel and one ECG channel. EEG had been recorded at frequency sampling ($F_s$ ) of 256 Hz whilst $F_s$ = 512 Hz for ECG.

### 4.2.2 Arousal Scoring

Sleep events such as arousals, oxygen desaturation, periodic leg movement, obstructive/central apnoea and hypopnoea were manually scored by a specialist according to the AASM criteria. Sleep stages were also detected and determined for almost all subjects based upon AASM sleep staging rules. Only arousal episodes longer than 3 seconds were considered for this study to meet AASM requirements of arousal scoring. Arousals were categorised into two groups based upon their duration, short-term arousal (STA) and long-term arousal (LTA). The STA term refers to arousal with duration less than 8 secs, whilst longer episodes were categorised as LTA.

We conducted classification of arousals regarding to their annotation files. Arousal might be induced by a respiratory episode or a limb movement event or non of them. If an arousal occurred 10 secs after the end of a respiratory event or 5 secs before the termination

of the event, it means that the induced arousal was associated with the adjacent respiratory event, then classified as RERA episode. Similarly, arousals related with any leg movement or periodic body movement episodes were categorised as movement arousals (MA). Once an arousal occurred simultaneously with both respiratory and movement events and the origin of arousal was unknown, the arousal was classified as RERA. If an arousal is neither associated to a respiratory event nor to a body movement episode, it was considered as spontaneous arousal.

Furthermore, we divided arousals into 5 sub-groups (NREM1, NREM2, NREM3, REM and Wake) regarding to the sleep stage that the arousal terminated. For instance, if an arousal started at stage NREM2 and ended at stage NREM1, it was categorised into NREM1 group. Table **4.1** presents a general view of how many arousals were scored and how they were classified. By these classifications, we could investigate the effect of arousal type, duration and sleep stage on cardiovascular dynamics once an arousal induces.

| Caregory | Class | Total Number (%) | Arousal number per subject Mean ± SD |
|---|---|---|---|
| Type | MA | 81886 (21.1%) | 30.7 ± 29.2 |
| | SA | 194648 (50.3%) | 73.1 ±37.9 |
| | RERA | 110576 (28.6%) | 41.5 ± 42.4 |
| Duration | STA | 146440 (37.8%) | 55.1 ± 36.9 |
| | LTA | 240670 (62.2%) | 90.4 ± 48.6 |
| Sleep Stage | NREM1 | 44262 (11.2%) | 16.6 + 13.3 |
| | NREM2 | 250031 (66.3%) | 93.9 ± 55.1 |
| | NREM3 | 9652 (2.5%) | 3.6 ± 6.2 |
| | REM | 51331 (12.3%) | 19.3 ± 13.5 |
| | Wake | 31033 (7.7%) | 11.7 ± 8.5 |

**Table 4.1:** General Information of total scored arousals in 2659 participants. *MA*, *SA* and *RERA* represent movement, spontaneous and respiratory effort related arousals, respectively. Short- and long-term arousal were represented by *STA* and *LTA* abbreviations.

#### 4.2.2.1 Arousal Indices

In any PSG reports, total number of arousal is significant to determine how much sleep was fragmented. As a result, the arousal index (*AI*) is defined as the total number of arousals

per one hour of sleep. This marker can estimate the degree of sleep fragmentation [20, 21]. Furthermore, respiratory disturbance index (*RDI*) is obtained as the total number of apnoea, hypopnoea and RERA events in one hour sleep. In addition, we defined movement arousal index (MAI), respiratory arousal index (*RAI*) and spontaneous arousal index (SAI) as the average number of MA, RERA and SA events in one hour of sleep, respectively. Thus, we calculated 5 arousal indices (*AI*, *RDI*, *MAI*, *RAI*, and *SAI*) regarding to each subject's number and types of sleep arousals as well as their total sleep time. Arousal indices allowed us to quantify the reciprocating pathological effect of arousals on cardiac intervals.

### 4.2.3 EEG Signal Processing

EEG spectral analysis is the gold standard for manual scoring of sleep events. Different EEG spectral power components vary when cardiovascular parameters suddenly change. These alteration can manifest as cortical events such as sleep arousals. The main aim of this section was to determine the exact location of arousal onset

#### 4.2.3.1 EEG Decomposition

As previously discussed, EEG signal is normally divided into frequency bands based on rhythmic activity. Since EEG is a non-stationary signal, traditional time-frequency transforms may not provide precise analysis. Thus, discrete wavelet transform (DWT) was applied to decompose EEG signal into spectral patterns. By this means the impact of non-stationarities on our analysis could be minimised. Since all EEG data was being recorded at $F_s$ = 256 Hz, we applied Daubechies wavelets with 8 vanishing moments to decompose EEG signals [151]. The DWT decomposed EEG into its frequency bands step-by-step in 7 levels (Figure **4.1**). During the initial levels ($d = 1, 2$), artefacts and noises were eliminated by DWT. At the fourth level, DWT provided power band component for frequencies between 16 and 32 Hz (beta wave). Similarly, we gained alpha, theta and delta bands at 5th, 6th and 7th level of DWT decomposition, correspondingly.

#### 4.2.3.2 Validation of Manual Scoring

It is essential to validate manual arousal scoring and verify arousal onset. Since we intended to investigate cardiac intervals variation at arousal onset, we had to find a strategy to determine the exact location of onset for each arousal. Thus, we referred to AASM basic definition for sleep arousals. According to the AASM criteria, only EEG shift greater than 16 Hz, can be considered as sleep arousals, except EEG spindles. All arousals were anal-

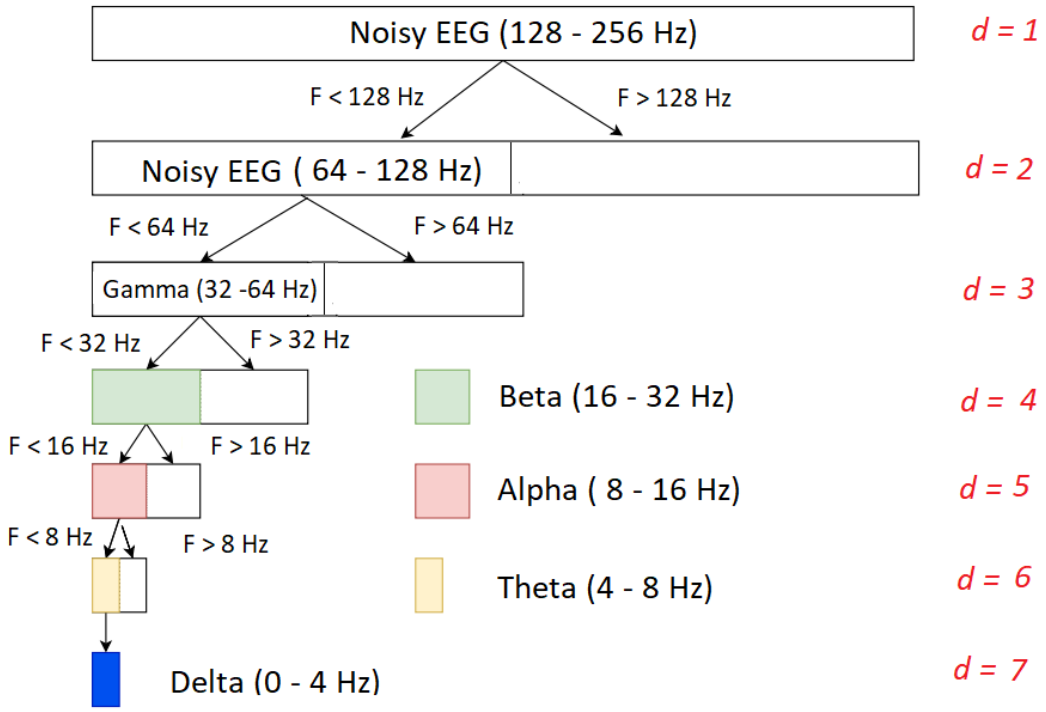



**Figure 4.1:** Graphical demonstration of EEG decomposition by Daubechies' Wavelet with 8 vanishing moments.

ysed to determine whether the manually scored arousal onset was precisely in accordance with EEG shift in frequencies greater than 16 Hz.

For arousal analysis, it was only required to focus on beta frequency band ($f \leq 16$) [152] and look for EEG shift. For each single arousal, two windows with different lengths were designed, the past window (PW) with length of 10 seconds and 3 seconds current window (CW). Both windows were being moved across the EEG signal, 3 seconds before and after arousal onset. By applying wavelet analysis, EEG beta power band was computed for the past and current windows. The beta power of both PW and CW could be calculated as follows:

$$Power_{\beta} = \frac{\sum_{f=16}^{f=32} p_f^2}{L} \tag{4.1}$$

We looked for the sudden EEG shift, the ratio of CW to PW beta power band then was computed. The highest $CW/PW$ ratio could indicate when EEG genuinely shifted and consequently, determined the precise moment of arousal onset. By this means, we assessed and then verified the onset index for all scored arousals in all subjects.

### 4.2.4 ECG Analysis

Any changes in the cardio-respiratory system can appear in ECG modulation. Alteration of ECG waves can therefore reveal an issue in cardio-respiratory function. We applied several ECG analysis methods to investigate subtle changes in cardiac time intervals once a sleep arousal occurs.

#### 4.2.4.1 Two-Dimensional Signal Warping

In biomedical signal analysis, matching and similarities can be quantified to detect subtle changes of time intervals. Schmidt *et al.* developed a two-dimensional signal warping (2DSW) algorithm for detection of subtle changes in noisy quasi-periodic biomedical signals [153]. The term of warping in signal and image processing is known once similarities of two pattern are compared. The developed 2DSW technique was integrated for measurement of QT beat-to-beat intervals variability and its performance was evaluated in simulations clinical data. The 2DSW approach could detect subtle changes in noisy ECG and have diagnostic potential for measuring repolarisation lability in patient suffering from myocardial infarction [153].

#### 4.2.4.2 Cardiac Time Intervals Measurement

For each single arousal, we defined cardiac arousal window (CAW) which contained ECG recording between 5 secs prior to and 10 secs after the verified arousal onset. It allowed us to precisely focus on cardiac function some moments before and after the arousal induces. Hence, for each subjects a matrix of 15 secs CAW time-series were generated.

We applied a 2DSW-based software for ECG analysis in our study. The software was a MATLAB graphical user interface (GUI) and automatically constructed an ECG template based upon several minutes ECG recordings [153]. The 2DSW GUI at the first step, generates the ECG template based upon an input ECG signal (Figure **4.2**) and then automatically estimates cardiac time intervals for another ECG recording based on developed template (Figure **4.3**). In each subject, an ECG recording sample with duration of 5 mins was randomly selected regardless of the sleep stage or the possibility of any sleep events such as arousal or apneic episodes. The ECG sample was the input of the 2DSW software to construct the ECG template that provided detailed information of ECG critical points indices such as $P_{onset}$, $P_{peak}$, $P_{offset}$, *QRS complex*, *R wave*, $T_{onset}$, $T_{peak}$ and $T_{offset}$ (Figure **4.2**).

For each subject, the matrix of CAW time-series was applied alongside with the sub-

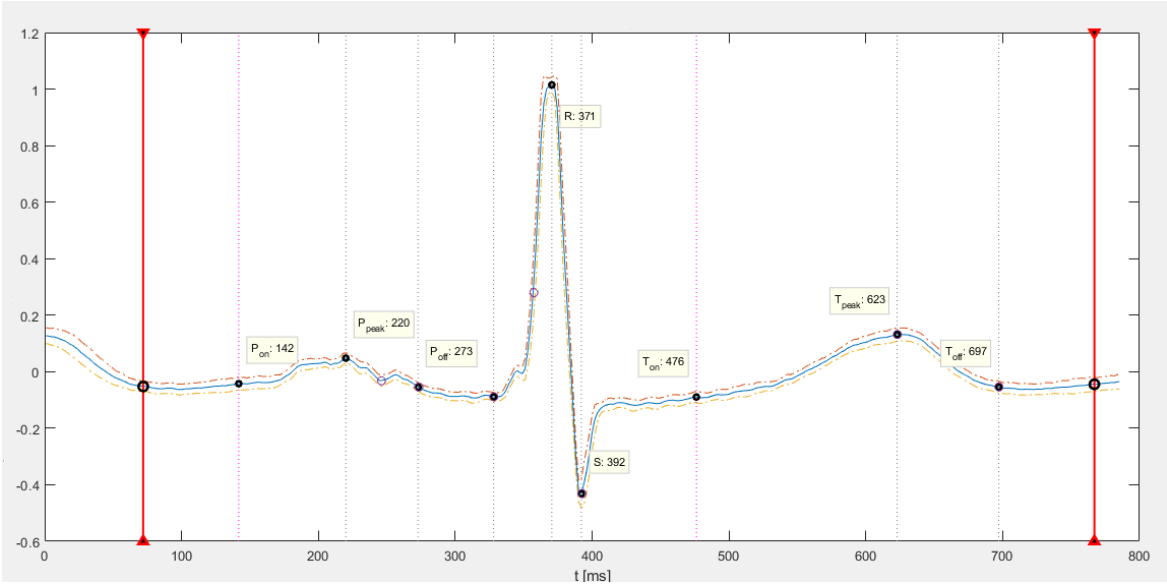



**Figure 4.2:** 2DSW software generated an ECG template using 5 minutes ECG recording.

ject's constructed template to estimate QT and RR time intervals through the 2DSW algorithm. The 2DSW GUI matched the template with each CAW time-series and estimated two main cardiac time intervals including the interval between two consecutive R waves or RR interval as well as the time delay between the start of QRS complex (Q-wave) and the end of T-wave which is known as QT interval. Figure **4.3** shows how 2DWS software could automatically measure QT for a typical ECG waveform in several steps.

Thus, two vectors of estimated QT and RR were produced for each CAW time-series, which represents cardiac intervals fluctuations pre- and post-onset of arousal. Each subject's QT and RR interval vectors were gathered together and constructed QT and RR interval matrices, respectively. By this means, we could obtain the cardiac intervals during almost all arousals in 2659 subjects.

### 4.2.5 Cardiac Intervals Signal Averaging

For each single arousal, QT and RR time series were obtained for 15 secs (5 seconds pre-onset and 10 secs post onset). The objective was to study how intervals vary arousal-by-arousal and subject-by-subject. The another question was whether different pathological sleep events that induced arousals were associated with QT and RR interval variability or not. In order to study the QT and RR variability subject-by-subject, the phased-rectified signal averaging algorithm was implemented. Then, we investigated whether averaging was an adequate approach to study cardiac intervals alterations.

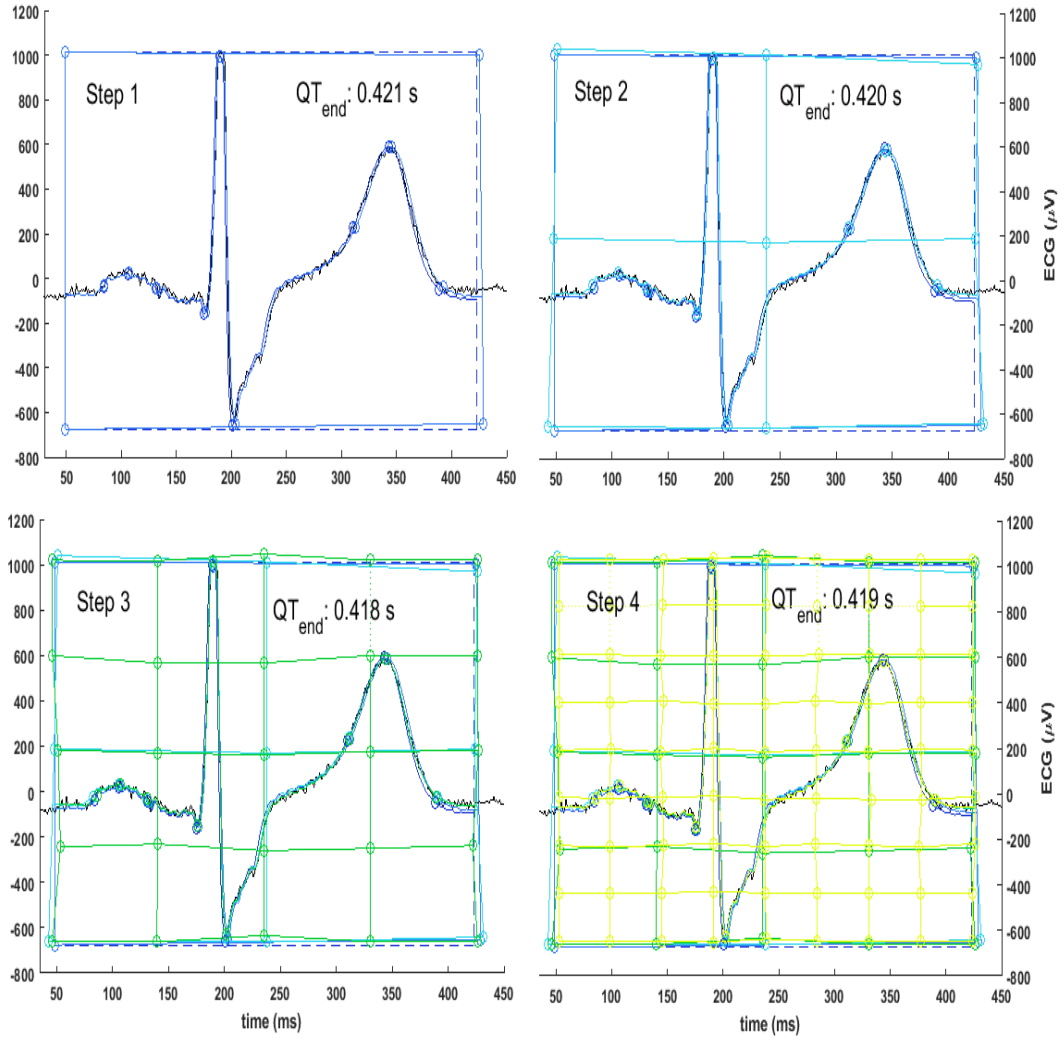



**Figure 4.3:** QT interval estimation for a typical ECG waveform using MATLAB-based 2DSW software in four steps.

#### 4.2.5.1 Phase-Rectified Signal Averaging

In 2006, Bauer *et al.* proposed phase-rectified signal averaging (PRSA) as a technique for analysis of quasi-periodic oscillations in noisy, non-stationary signals. The suggested method was based on the definition of anchor points in the signal and then using them to align and phase-rectify the oscillatory fluctuations followed by an averaging of the surroundings of the anchor points [154]. PRSA algorithm can briefly be described as following:

i) Let $X = \{ x_1, x_2, ...,x_N \}$ be a long time series representing the signal which may contain non-stationarities, noise or artefacts.

ii) Anchor points in $X$ defined according to the specific features such as increasing ($x_i > x_{i-1}$) or decreasing ($x_i < x_{i-1}$)

iii) Windows and surroundings, of length 2L around each anchor point $x_{iv}$ where $v$ = 1 , . . . , $M$, are identified. $M$ is the total number of regarded anchor points. The surrounding of $x_{i_v}$ is $x_{i_v-L}$ , $x_{i_v-L+1}$ , . . . ,$x_{i_v}$ , . . . , $x_{i_v-L-2}$ , $x_{i_v-L-1}$.

iv) Window are aligned at their anchor points, $x_{i_v}$ and $PRSA_x$ is obtained by averaging all windows:

$$PRSA_x(k) = \bar{x}(k) = \frac{1}{M}\sum_{v=1}^{M} x_{i_v+k} \tag{4.2}$$

where $k$ = *–L,...,0,..., L – 1*.

In this study, we applied PRSA technique for averaging of QT and RR intervals in a subject. We consider arousal onset as anchor points and computed the $PRSA_{RR}$ and $PRSA_{QT}$ as following:

$$PRSA_{RR}(k) = \frac{1}{M}\sum_{v=1}^{M} rr_{i_v+k} \tag{4.3}$$

and

$$PRSA_{QT}(k) = \frac{1}{M}\sum_{v=1}^{M} qt_{i_v+k} \tag{4.4}$$

where $M$ is the number of detected arousals of a subject, $rr_{iv}$ and $rr_{qt}$ are the RR and QT interval at arousal onset or just before it.

Figure **4.4** shows an example of how we developed $PRSA_{QT}$ and $PRSA_{RR}$. For each subject, $PRSA_{QT}$ and $PRSA_{RR}$ presented an average of QT and RR variability pre- and post-onset of sleep arousals.

### 4.2.5.2 Bivariate PRSA

PRSA, usually known as univariate PRSA, has been generally used to rectify the phase of a noisy quasi-periodic signal. Schumann *et al.* proposed a new modification of univariate PRSA for investigation on the inter-relations between two signals [155]. In bivariate PRSA (BPRSA) algorithm, we have two signals, trigger signal, $X = \{ x_1, x_2, ...,x_N \}$ and target signal, $Y = \{ y_1, y_2, ...,y_N \}$ . Anchor points $i_1$,...,$i_M$ are defined for any increase or decrease in trigger signal, while surrounding are defined and averaged for the target signal. Thus BPRSA as the phase rectified averages for $X \rightarrow Y$ computed as following:

$$BPRSA_{X\rightarrow Y}(k) = \bar{y}(k) = \frac{1}{M}\sum_{v=1}^{M} y_{i_v+k}, \tag{4.5}$$

where $k$ = *–L,...,0,..., L – 1*.

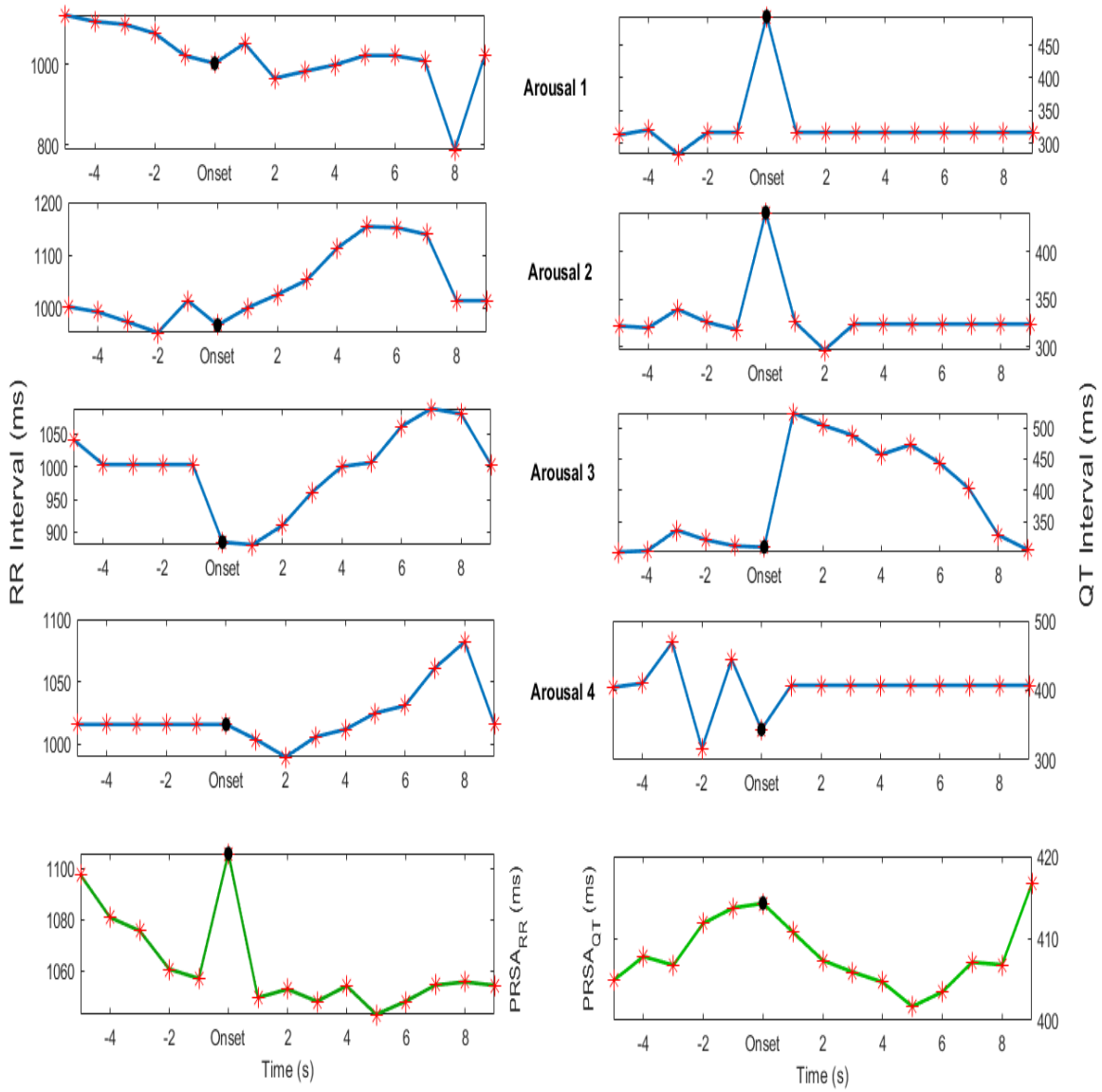



**Figure 4.4:** A graphical demonstration of (**Left**) RR interval phase-rectified signal averaging ($PRSA_{QT}$) and (**Right**) QT interval phase-rectified signal averaging ($PRSA_{RR}$) for a subject with 149 sleep arousals. Arousal onsets (black points) was appointed as anchors.

BPRSA is a non-symmetric algorithm that means if the trigger and target signals are swapped, the outcomes, $BPRSA_{X\to Y}$ and $BPRSA_{Y\to X}$ will be different [155].

Once an arousal occurs, both RR and QT intervals are expected to change immediately. To find out whether increase in one cardiac interval will result to increase or decrease of another one, we investigated on inter-relations between QT and RR. BPRSA assisted us to model cardiac inter-relations during the arousal. $BPRSA_{QT\to RR}$ and $BPRSA_{RR\to QT}$ were estimated to assess how those parameters are inter-related. Our algorithm for BPRSA

analysis of QT and RR was as following:

i) Let $QT = \{ qt_1, qt_2, ...,qt_N \}$ and $RR = \{ rr_1, rr_2, ...,rr_N \}$ and are two time series of QT and RR intervals of 5 seconds pre- and 10 second post arousal onset, after re-sampling at $F_s$ = 10 Hz.

ii) Anchors for $RR_i$ are defined as the peaks points adjacent to onset. It indicates when the RR was considerably increasing. Then the anchors should be assigned in $QT_i$ curve to compute $BPRSA_{RR\rightarrow QT}$ for a subject as following:

$$BPRSA_{RR\rightarrow QT}(k) = \frac{1}{M}\sum_{v=1}^{M} QT_{i_v+k}, \tag{4.6}$$

where $M$ is the number of detected arousals of a subject.

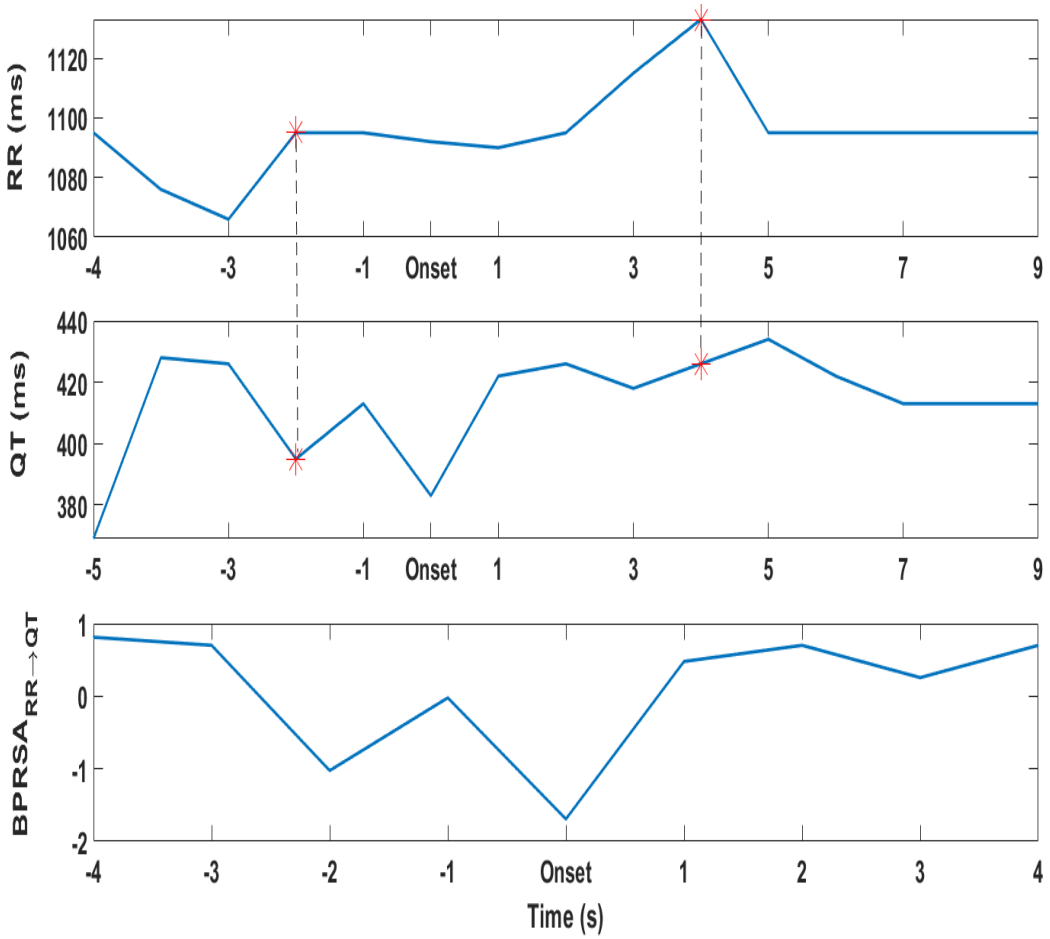



**Figure 4.5:** Illustrations of implementing bivariate PRSA of RR and QT mutual relations during an arousal occurrence. Anchors of *RR* (red points) were determined and then transferred into *QT*. An average of anchors and surroundings estimated the normalised $BPRSA_{RR\rightarrow QT}$, 4 seconds pre- and post- onset.

Figure **4.5** graphically illustrates how BPRSA algorithm was launched for estimation of QT and RR inter-relations in a particular cardiac arousal window. Anchors of *RR* indicates when RR interval curve was significantly increasing. In this arousal, the algorithm found 4 anchors in *RR* curve, though in the most of arousals, maximum two anchors were found according to the algorithm. By averaging the anchors and surroundings after transferring anchors to *QT*, the $BPRSA_{RR\rightarrow QT}$ for the arousal was obtained and describes whether an increase in RR interval was accompanied with a shift in QT interval at onset or moments before and after it. At the end, we normalised $BPRSA_{RR\rightarrow QT}$ using mean and standard deviation of QT interval in each subject.

Similarly, if we assume *QT* as trigger signal and *RR* as target, $BPRSA_{QT\rightarrow RR}$ can be computed. The peak points of *QT* indicate when QT interval curve was increasing and defined as anchors and assigned at *RR* to estimate $BPRSA_{QT\rightarrow RR}$ :

$$BPRSA_{QT\rightarrow RR}(k) = \frac{1}{M}\sum_{v=1}^{M} RR_{i_v+k}, \tag{4.7}$$

BPRSA analysis allowed to investigate whether instantaneous fluctuations in QT intervals during arousal are in the same direction with RR variations. Figure **4.6** presented an example of how we reapplied BPRSA algorithm to model $BPRSA_{QT\rightarrow RR}$. Exchanging of *QT* and *RR* will result two different curves where $BPRSA_{QT\rightarrow RR}$ and $BPRSA_{RR\rightarrow QT}$ could have some common features and correlation, however they both model the variations in two different signals and they do not have necessarily same trends. In addition, the variability of both $BPRSA_{QT\rightarrow RR}$ and $BPRSA_{RR\rightarrow QT}$ in different subjects and different types of arousals can reveal the *QT/RR* inter-relations before, during and after arousal occurrence.

By using univariate and bivariate PRSA, we obtained four time-series curves for each subjects, $PRSA_{QT}$, $PRSA_{RR}$, $BPRSA_{QT\rightarrow RR}$ and $BPRSA_{RR\rightarrow QT}$. At the next step, the variability of these curves at arousal onset, before and after it were investigated to find out how an induced arousal influences on cardiac time intervals as well as cardiovascular system.

### 4.2.6 Cardiac Interval Gradients

To study whether cardiac intervals were increasing or decreasing once an arousal occurred, we defined QT and RR gradients. The gradient of a curve manifests its slope at a particular point and it can be different at another point of the curve. The gradient of a cardiac time interval e.g. QT, may show its trend at a particular time as well as its instantaneous changes

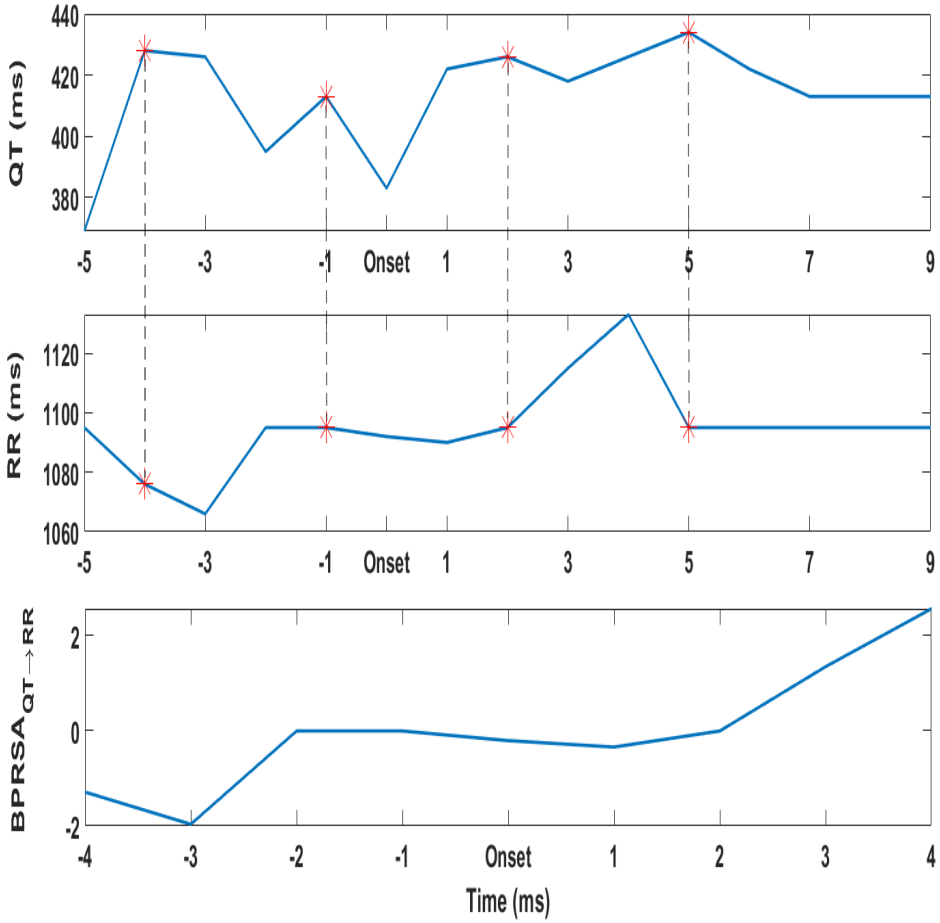



**Figure 4.6:** A graphical demonstration of using $QT$ as trigger and $RR$ as target signals to estimate $BPRSA_{QT \rightarrow RR}$ for a particular arousal. Normalised $BPRSA_{QT \rightarrow RR}$ can be easily obtained using mean and standard deviation of RR in each subject.

over the time. Our algorithm to compute the gradient of cardiac time interval during arousal time was as following:

Let $X = \{ x_{-5},...,x_{-4},..., x_{onset},...,x_1,..., x_5 \}$ be a discrete time-series which can be a cardiac arousal window or a PRSA interval curve that includes interval values from 5 seconds prior to onset to 5 seconds after it. Then gradients be defined as:

$$Gr_{-4} = (x_{-4} - x_{-5}); \qquad Gr_{-3} = (x_{-3} - x_{-4});$$

$$Gr_{-2} = (x_{-2} - x_{-3}); \qquad Gr_{-1} = (x_{-1} - x_{-2});$$

$$Gr_0 = (x_0 - x_{-1}); \qquad Gr_1 = (x_1 - x_0);$$

$$Gr_2 = (x_2 - x_1); \qquad Gr_3 = (x_3 - x_2);$$

$$Gr_4 = (x_4 - x_3); \qquad Gr_5 = (x_5 - x_4);$$

Hence, the gradient vector $GR$ = [$Gr_{-4}$, $Gr_{-3}$, $Gr_2$, $Gr_{-1}$, $Gr_0$, $Gr_1$, $Gr_2$, $Gr_3$, $Gr_4$,

$Gr_5$] could be obtained. The $Gr_i < 0$ indicates that cardiac interval, $'X'$ had a downward trend and was decreasing. While positive $Gr_i$ reflects $'X'$ increasing. For instance, if $Gr_1 <$ 0, it is interpreted that the time interval shortened right after onset (Figure **4.7**).

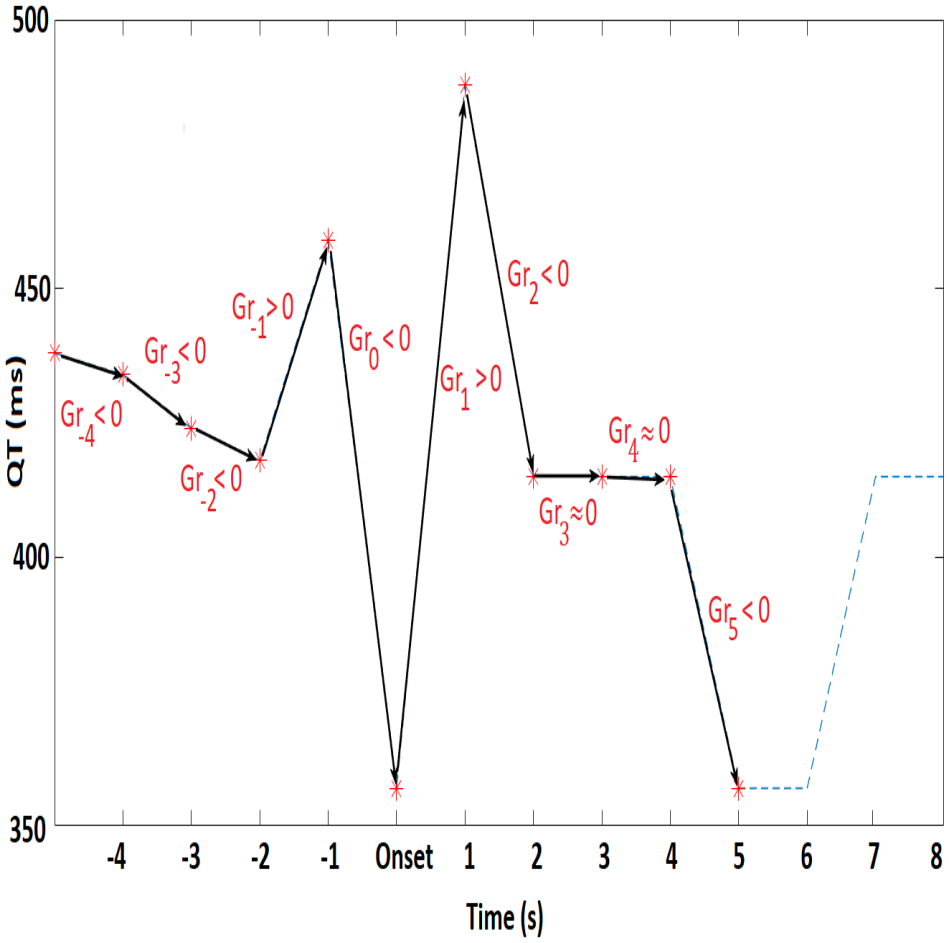



**Figure 4.7:** A graphical demonstration QT gradients computation. $Gr_{-4}$, $Gr_{-3}$, $Gr_{-2}$, $Gr_{-1}$ and $Gr_0$ are pre-onset gradients and $Gr_4$, $Gr_1$, $Gr_2$, $Gr_3$, $Gr_4$ and $Gr_5$ are post-onset gradients.

### 4.2.7 Cardiac Intervals Variability

To investigate the variability of cardiac intervals during arousal inducing in different subjects, we developed all 2569 participants $PRSA_{QT}$ and $PRSA_{RR}$ curves and then computed the following statistical features for all:

i) *QT and RR range*: the difference between the maximum and minimum of $PRSA_{QT}$ either 5 seconds before onset ($Pre_{rangeQT}$) or 10 seconds after it $Post_{rangeQT}$. The RR range for pre ($Pre_{rangeRR}$) and post-onset ($Post_{rangeRR}$ )windows could be derived from $PRSA_{RR}$ just similar to QT range.

ii) *QT and RR mean*: we computed $Pre_{meanQT}$, $Post_{meanQT}$, $Pre_{meanRR}$ and $Post_{meanRR}$ as the mean of $Pre-QT$, $Post-QT$, $Pre-RR$ and $Post-RR$ vectors, respectively.

iii) *QT and RR Variance*: $Pre_{VarQT}$, $Post_{VarQT}$, $Pre_{VarRR}$ and $Post_{VarRR}$ indicated the variance of QT and RR before and after onset.

iv) In addition, we computed $QTV_{i-Pre}$ and $QTV_{i-Post}$ for pre- and post-onset based on Berger *et al.* [156]:

$$QTV_i = log(\frac{VarQT/(meanQT)^2}{VarRR/(meanRR)^2}), \tag{4.8}$$

where $VarQT$ and $meanQT$ were variance and mean of QT interval vectors. Likewise, $meanRR$ and $VarRR$ represent mean and variance of RR interval vectors.

v) *QT/RR Slope*: The measures $Pre_{Slope}$ and $Post_{Slope}$ represents the slope of a linear regression function fitted QT and RR before and after onset. The Slope reflects mutual changes of QT and RR intervals

vi) *QT/RR* $R^2$: Residual of the regression line fitted to QT and RR ($Pre_{R^2}$ and $Post_{R^2}$). This factor indicates the strength of the QT/RR dependence.

### 4.2.8 Statistical Analysis

We applied different statistical and graphical analysis methods to study QT and RR interval variations before and after arousal occurrence. Visualisation of gradients allowed us to investigate momentary changes in cardiac intervals once arousal occur. Statistical measures like mean and variance utilised the comparison of pre- and post-onset situations. The Pearson linear correlation coefficient was also used to assess any possible associations between computed parameters. We also applied the Student's t-test and ANOVA analysis to evaluate whether obtained results are statistically significant.

## 4.3 Results

### 4.3.1 Cardiac Interval Gradients

Gradients of cardiac intervals can detect the instantaneous changes in intervals. The direction of $Gr_i$ determines whether the time interval had an upward or downward trend at moment of $i$. The absolute value of $Gr_i$ reveals the intensity of changes. We analysed gradients in two ways, subject-by-subject and arousal-by-arousal. In order to investigate how cardiac interval gradients changes subject-by-subject, we estimated all participants $PRSA_{QT}$

and $PRSA_{RR}$ time-series and then computed their gradients. In each subject, two gradient vectors were obtained, $Gr(PRSA_{QT})$ and $Gr(PRSA_{RR})$ which respectively represented the gradient analysis of $PRSA_{QT}$ and $PRSA_{RR}$.

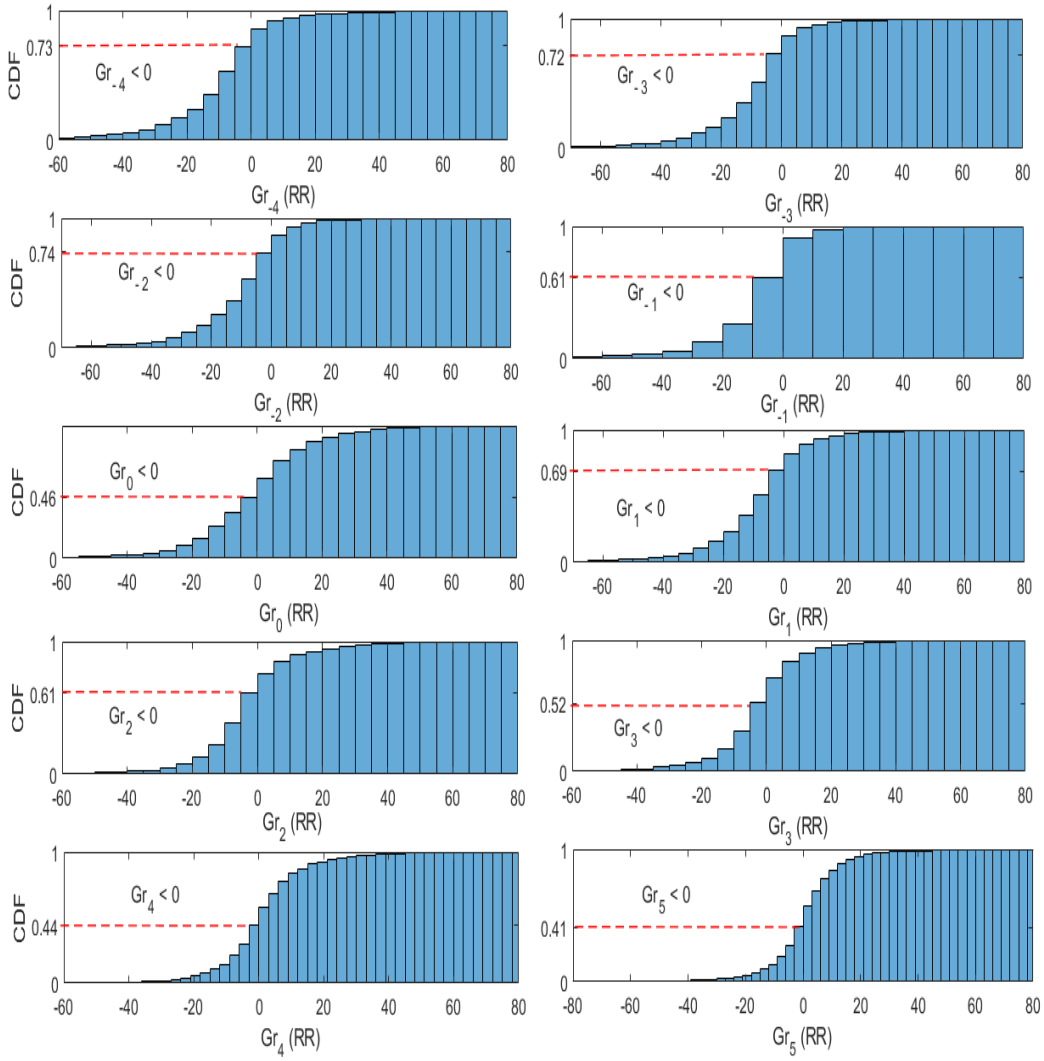



**Figure 4.8:** The histogram of cumulative distribution function (CDF) for gradients of $PRSA_{RR}$ in 2659 subjects. The probabilities of $Gr_i < 0$ has been indicated in sub-figures.

To investigate how $Gr_i$ values were distributed, we used the cumulative distribution function (CDF) as the measure of probability distribution of $Gr_i$. By this means, we could estimate the likelihood of $Gr_i < 0$, the marker of interval reduction. The CDF of $PRSA_{RR}$ gradients was depicted in Figure **4.8**. In each histogram, the distribution of $Gr_i$ based upon their probability was indicated. For instance, the $CFD(Gr\_4 < 0) = 0.73$, $CFD(Gr\_3 < 0) = 0.72$, $CFD(Gr\_2 < 0) = 0.74$ and $CFD(Gr\_1 < 0) = 0.61$ indicate that until 2 seconds

prior to arousal onset, the RR interval was decreasing with probability greater than 70%. This likelihood dropped to 61% one moment to before arousal induces. Furthermore, the $PRSA_{RR}$ dropped at onset in 46% and this means the chance of RR shortening reduced at arousal onset. The early post-onset gradients, $CFD(Gr_1 < 0) = 0.69$ and $CFD(Gr_2 < 0) = 0.61$ also demonstrates that RR is more likely to shorten than prolong even 2 seconds after arousal onset. Vice versa, the CDF analysis of later gradients ($Gr_3$, $Gr_4$ and $Gr_5$) show that the RR was likelier to have ascending trend than descending.

We also visualised cumulative distribution of $PRSA_{QT}$ gradients in all participants (Figure **4.9**). An overview of gradients in $PRSA_{QT}$ indicates that in at least 60% of subjects, QT had a descending trend moments before and after arousal occurs. The only exception was $CFD(Gr_0 < 0) = 0.57$, which means that the probability of QT shortening at arousal onset was less than moments prior to or following to onset. Even 5 seconds after onset, $CFD(Gr_0 < 0) = 0.71$ that indicates a post-arousal continuous QT shortening.

PRSA algorithm provided a precise average of QT and RR intervals in a subject. According to the literature, using anchors and average could help to minimise the effects of noises and missing points. It also enabled us to compare cardiac changes during arousals in different subjects. However, PRSA analysis does not allow to understand a particular single arousal behaviour. Moreover, we are not able to compare cardiac changes in one arousal with another arousal. To investigate arousal-by-arousal cardiac interval gradients, we computed gradients for all arousals of all subjects, regardless of its type or duration instead of computation of gradients for PRSA curves. We previously, created CAW vector for each single arousal and used it to compute gradient vector for all arousals. Thus, RR and QT interval gradients were computed for all arousals. As a consequence, we reached two same-sized matrices, $Gr(QT)$ and $Gr(RR)$, which had 387110 rows as the number of all arousals and 10 columns represented 10 $Gr_i$. In each arousal, the gradients of QT and RR were computed and whether they were negative, positive or zero determined they were descending ($\downarrow$), ascending ($\uparrow$) or constant and with no change ($N.C$). The aim was to investigate on $Gr(QT)$ and $Gr(RR)$ analysis and compare them with $Gr(PRSA_{QT})$ and $Gr(PRSA_{RR})$. Tables **4.2** and **4.3** illustrated the percentage of arousal with ascending, descending or no change $Gr_i$. Tables also presents a comparison of RR and QT interval gradients in three arousal groups (MA, SA and RERA) as well as in short- and long-term arousals.

As shown in Table **4.2**, gradients trend distribution is independent of arousal type or

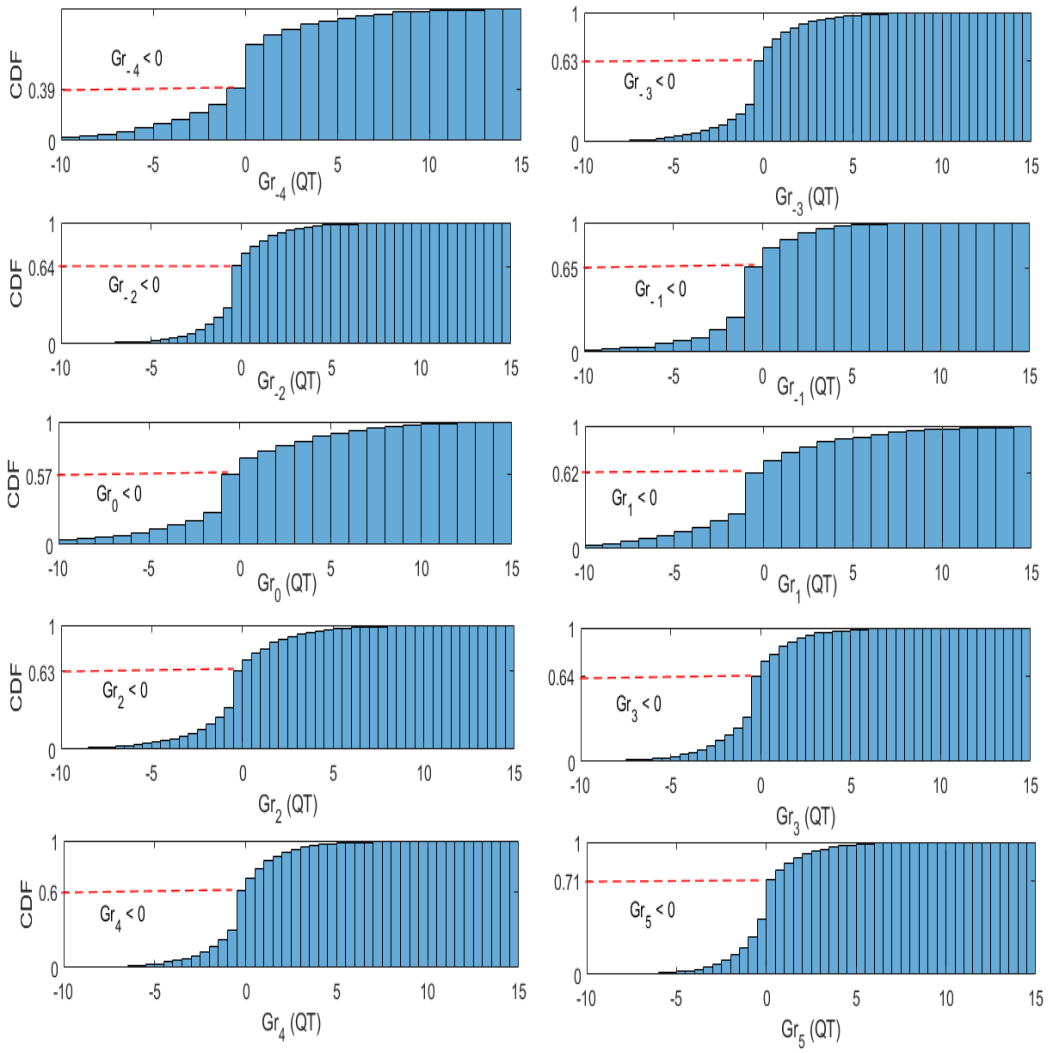



**Figure 4.9:** The CDF histogram of gradients for QT time intervals.

duration. For instance, $Gr_{-1}$ refer the slope of QT curve one second prior to arousal onset. Only 17.9% of all arousals had a descending QT (↓) at moment right before the onset. This percentage in MA, SA and RERA arousal group was 15.4%, 17.6% and 17.4%, respectively. Similarly, the probability of negative gradient at onset-1 in short and long duration arousal was very close (17.5% vs 17.3%). The percentage of zero ($N.C$) and ascending gradients also had the same conditions. At arousal onset, QT gradients were distributed in three groups with almost same probability. The chance of QT drop at a typical arousal was approximately as same as QT rise. The likelihood of no change in QT at onset was also same. In this case, there is no convincing evidence to explain QT behaviour at arousal onset. The probability of $Gr_i = 0$ ($N.C(\%)$) was gradually increasing over the time after arousal onset. One second after onset, the probability of no change $Gr_1$ was only 29.4%,

which means in more than 70% of arousal QT changed at one second after onset. However one second later in almost half of all arousal, QT did not change at all ($Gr_2 = 0$). The probability no changes at 3, 4 and 5 seconds after onset ($Gr_i = 0$, $i = 3,4,5$) were 57.3%, 61,6% and 63.6%, respectively. This demonstrates the post-onset gradual QT smoothing. A comparison between results shown in Figure **4.9** and Table **4.2** indicates a clear difference between obtained results from $Gr(PRSA_{QT})$ and $Gr(QT)$. The averaging algorithm provided an overview of QT and RR activation and its outcome is not necessarily reflects the cardiovascular activation during each single arousal.

Analysis of RR interval gradients of all arousals shows that the trend of changes in RR pre and post-arousal moments does not seem to be depended to type or duration of arousal. While the probability of RR shortening at onset ($Gr_0 \downarrow$) of all arousal was 28.5%, this ratio in MA, SA and RERA episodes was 30.6%, 29.3% and 28.3%, receptively. Although, shorter episodes are likelier to be accompanied with RR interval drop at onset than longer arousal by about 3% (Table **4.3**).

Similar to QT gradients, the percentage of RR no-change gradients had an ascending trend after onset. For example , the zero gradient at onset of RERA events had 42.7% chance to be unchanged, this likelihood reached to 51.6%, three seconds later and shifted to 54.5% five seconds after onset.

Beyond $Gr_i$ direction, as an indicator of the trend of instantaneous changes in cardiac intervals, the scalar value of $Gr_i$ which represents the rate of change were investigated in different arousal categories. Hence, we compared cardiac intervals $Gr_i$ variability in terms of their type (MA, SA and RA), duration (STA and LTA) and the sleep stage of arousal termination (Table **4.4**). We applied the two sample t-test to investigate whether variability of QT and RR $Gr_i$ is related to the duration of arousal or not (significance level: $p = 0.05$). Furthermore, the one-way ANOVA analysis assessed whether arousal type or sleep stage affect on momentary changes in QT and RR intervals. The significant level for $Gr_i$ analysis based on arousal type was $p = 0.05$, whilst it was considered $p = 0.01$ for investigation on sleep stages. The post hoc Tukey's honest significant difference criterion was also applied after ANOVA analysis to determine the gradients in which type of arousals or sleep stages were significantly different.

| $Gr_i$ | | All | MA | SA | RERA | STA | LTA |
|---|---|---|---|---|---|---|---|
| | Number | 387110 | 81886 | 194648 | 110576 | 146440 | 240670 |
| $Gr_{-4}$ | $\uparrow(\%)$ | 34.4 | 33.3 | 33.4 | 33.8 | 33.3 | 33.4 |
| | $\downarrow(\%)$ | 34.1 | 33 | 33.1 | 33.5 | 33.1 | 33.1 |
| | $N.C(\%)$ | 31.5 | 33.7 | 33.4 | 32.6 | 33.7 | 33.5 |
| $Gr_{-3}$ | $\uparrow(\%)$ | 22.6 | 21.5 | 22.2 | 22.3 | 21.9 | 22.1 |
| | $\downarrow(\%)$ | 22.7 | 21.8 | 22.3 | 22.3 | 21.9 | 22.2 |
| | $N.C(\%)$ | 54.6 | 56.6 | 55.6 | 55.4 | 56.2 | 55.7 |
| $Gr_{-2}$ | $\uparrow(\%)$ | 19.1 | 18.3 | 18.8 | 18.8 | 18.5 | 18.6 |
| | $\downarrow(\%)$ | 19.6 | 18.8 | 19.3 | 19 | 19.1 | 19 |
| | $N.C(\%)$ | 61.3 | 63 | 62 | 62.2 | 62.4 | 62.4 |
| $Gr_{-1}$ | $\uparrow(\%)$ | 17.1 | 16.3 | 16.9 | 16.7 | 16.7 | 16.6 |
| | $\downarrow(\%)$ | 17.9 | 17.4 | 17.6 | 17.4 | 17.5 | 17.3 |
| | $N.C(\%)$ | 65 | 66.3 | 65.5 | 66 | 65.8 | 66 |
| $Gr_0$ | $\uparrow(\%)$ | 33.1 | 31.9 | 32.3 | 32.5 | 32 | 32.1 |
| | $\downarrow(\%)$ | 34.4 | 33.6 | 33.5 | 33.8 | 33.5 | 33.4 |
| | $N.C(\%)$ | 32.4 | 34.5 | 34.3 | 33.7 | 34.5 | 34.4 |
| $Gr_1$ | $\uparrow(\%)$ | 35.7 | 34.5 | 34.6 | 35.2 | 34.4 | 34.8 |
| | $\downarrow(\%)$ | 35 | 34 | 34.2 | 33.9 | 34.1 | 33.8 |
| | $N.C(\%)$ | 29.4 | 31.5 | 31.2 | 30.9 | 31.5 | 31.5 |
| $Gr_2$ | $\uparrow(\%)$ | 25.2 | 24.3 | 24.7 | 24.4 | 24.8 | 24.2 |
| | $\downarrow(\%)$ | 25.6 | 24.5 | 25.3 | 24.9 | 25 | 24.8 |
| | $N.C(\%)$ | 49.2 | 51.1 | 50.1 | 50.7 | 50.1 | 51 |
| $Gr_3$ | $\uparrow(\%)$ | 21.2 | 20.2 | 21.1 | 20.4 | 21.2 | 20.2 |
| | $\downarrow(\%)$ | 21.5 | 20.8 | 21.2 | 20.8 | 21.1 | 20.8 |
| | $N.C(\%)$ | 57.3 | 59 | 57.8 | 58.8 | 57.7 | 59 |
| $Gr_4$ | $\uparrow(\%)$ | 19.2 | 18.7 | 19.1 | 18.4 | 19.5 | 18.3 |
| | $\downarrow(\%)$ | 19.2 | 18.2 | 19 | 18.5 | 18.8 | 18.5 |
| | $N.C(\%)$ | 61.6 | 63 | 61.9 | 63.1 | 61.7 | 63.2 |
| $Gr_5$ | $\uparrow(\%)$ | 18.3 | 17.8 | 18.2 | 17.4 | 18.4 | 17.4 |
| | $\downarrow(\%)$ | 17.9 | 16.9 | 17.8 | 17.4 | 17.6 | 17.3 |
| | $N.C(\%)$ | 63.9 | 65.3 | 64.1 | 65.2 | 64 | 65.3 |

**Table 4.2:** QT interval gradients analysis in different arousal categories based on arousal types (**MA**, **SA** and **RERA**) and duration (**STA** and **LTA**). **LTA** and **STA** represent long- and short-term arousal. The percentage of ascending and descending gradients were represented by $\uparrow$ and $\downarrow$ signs. **N.C** refers to zero gradients.

#### 4.3.1.1 Gradients and Arousal Types

As tabulated in Table **4.4**, RR $Gr_i$ variability are more associated to arousal type than QT $Gr_i$ variability. Only QT gradients at 1 sec and 4 secs after onset significantly differed by arousal type. The post hoc test shows that QT gradients one second after arousal onset

| $Gr_i$ | | All | MA | SA | RERA | STA | LTA |
|---|---|---|---|---|---|---|---|
| | Number | 387110 | 81886 | 194648 | 110576 | 146440 | 240670 |
| $Gr_{-4}$ | $\uparrow(\%)$ | 22.6 | 22.3 | 23.1 | 22.5 | 23 | 22.7 |
| | $\downarrow(\%)$ | 29.6 | 30.3 | 30.3 | 30 | 30.3 | 30.4 |
| | $N.C(\%)$ | 47.8 | 47.4 | 46.6 | 47.5 | 46.7 | 46.9 |
| $Gr_{-3}$ | $\uparrow(\%)$ | 20.4 | 19.8 | 21.1 | 20.1 | 20.7 | 20.5 |
| | $\downarrow(\%)$ | 29.2 | 30.3 | 29.7 | 30 | 30 | 30.1 |
| | $N.C(\%)$ | 50.4 | 49.9 | 49.1 | 49.9 | 49.2 | 49.4 |
| $Gr_{-2}$ | $\uparrow(\%)$ | 18.2 | 17.7 | 19 | 17.9 | 18.8 | 18.3 |
| | $\downarrow(\%)$ | 27.1 | 28.5 | 27.7 | 28 | 28 | 28.2 |
| | $N.C(\%)$ | 54.7 | 53.8 | 53.3 | 54.1 | 53.2 | 53.6 |
| $Gr_{-1}$ | $\uparrow(\%)$ | 15.8 | 16.2 | 15.9 | 15.9 | 16.4 | 15.8 |
| | $\downarrow(\%)$ | 17.4 | 19 | 18.4 | 18.5 | 18.7 | 18.8 |
| | $N.C(\%)$ | 66.8 | 64.8 | 65.6 | 65.6 | 64.9 | 65.3 |
| $Gr_0$ | $\uparrow(\%)$ | 28.4 | 27 | 28.7 | 28.9 | 27 | 29.3 |
| | $\downarrow(\%)$ | 28.5 | 30.6 | 29.3 | 28.3 | 31.4 | 28.2 |
| | $N.C(\%)$ | 43.1 | 42.4 | 42 | 42.7 | 41.5 | 42.5 |
| $Gr_1$ | $\uparrow(\%)$ | 20.9 | 20.9 | 21.8 | 20.4 | 22.3 | 20.6 |
| | $\downarrow(\%)$ | 31.1 | 31.6 | 31.9 | 31.5 | 31.9 | 31.8 |
| | $N.C(\%)$ | 47.9 | 47.4 | 46.3 | 48.1 | 45.8 | 47.6 |
| $Gr_2$ | $\uparrow(\%)$ | 22.1 | 23 | 22.8 | 21.3 | 24.4 | 21.3 |
| | $\downarrow(\%)$ | 28.5 | 28.3 | 29.4 | 28.9 | 28.6 | 29.4 |
| | $N.C(\%)$ | 49.2 | 51.1 | 50.1 | 50.7 | 50.1 | 51 |
| $Gr_3$ | $\uparrow(\%)$ | 22.8 | 24.4 | 23.7 | 21.7 | 25.9 | 21.8 |
| | $\downarrow(\%)$ | 26 | 25.2 | 26.8 | 26.7 | 25.5 | 27.2 |
| | $N.C(\%)$ | 51.2 | 50.4 | 49.5 | 51.6 | 48.6 | 51 |
| $Gr_4$ | $\uparrow(\%)$ | 24 | 26 | 24.9 | 22.6 | 27.5 | 22.8 |
| | $\downarrow(\%)$ | 23.2 | 22 | 24 | 24.2 | 22.2 | 24.7 |
| | $N.C(\%)$ | 52.8 | 51.9 | 51.1 | 53.1 | 50.3 | 52.5 |
| $Gr_5$ | $\uparrow(\%)$ | 24.3 | 26.4 | 25 | 23.3 | 27.5 | 23.3 |
| | $\downarrow(\%)$ | 21.5 | 20.2 | 22.4 | 22.3 | 20.5 | 22.9 |
| | $N.C(\%)$ | 54.2 | 53.4 | 52.6 | 54.5 | 52.1 | 53.8 |

**Table 4.3:** RR interval gradients analysis in different arousal categories based on arousal types

in respiratory arousals was significantly different from spontaneous arousal. On the other hand, $Gr_i$ of RR intervals in almost all $i$ moments were associated with arousal type, except $i$=1. The post hoc test results indicates that gradients at $i$= *onset, onset+2, onset+3 and onset+4* ($Gr_0, Gr_2, Gr_3$, $Gr_4$) were significantly associated with arousal type. This means post arousal RR momentary changes are related to arousal type as consequently to sleep event which induced the arousal.

#### 4.3.1.2 Gradients and Arousal Duration

The duration of arousal played a significant role in gradients RR variability in all $Gr_i$, except $i = -4$ (Table **4.4**). This means the RR pre-and post-onset instantaneous changes in arousal with duration shorter than 8 secs were significantly different from the longer arousals. Vice versa, our findings did not show a significant dependency of QT $Gr_i$ variability and arousal duration, except $Gr_{-4}$ and $Gr_1$.

#### 4.3.1.3 Gradients and Sleep Stage

The RR fluctuations during arousal were associated to sleep stages. The pre-onset RR gradients of arousals ended in wake stage ($Gr_{-3}$, $Gr_{-2}$ and $Gr_{-1}$) were significantly different from arousals ended to stage NREM1, NREM2 or REM. Furthermore, RR gradients in arousals occurred at NREM3 stage had a different variability with arousal occurred in other sleep stages. QT gradients of REM arousals at onset and one moment later ($Gr_0$ and $Gr_1$) significantly differed from arousals occurred as stage 2. This shows QT gradients were independent of RR gradients, because QT and RR instantaneous changes in various sleep stages were not related to each other.

### 4.3.2 Cardiac Intervals Variability Analysis

To analyse how much arousal can affect cardiac intervals, we defined and applied statistical parameters. By this means, we estimated the variability of QT and RR interval 5 seconds before an arousal occurs, as well as 10 seconds after arousal inducing. An analysis of extracted parameters pre- and post-onset of arousals quantified changes in cardiac intervals during arousal events. Table **4.5** illustrated a comparison of cardiac measures before and after arousal onset. Features extracted from $PRSA_{RR}$ and $PRSA_{QT}$ represented the intervals variability in 2659 subjects. Obviously a feature would vary after arousal induces. To evaluate whether the difference in features pre- and post- arousal onset was statically significant, we applied the paired t-test. The linear correlation ratios of pre- and post-onset features were demonstrated in table.

According to our findings, the average range of both RR and QT intervals were considerably increasing after arousal onset. The range of a time series indicates how spread out values of a time series. Thus, a greater range means greater data dispersion. Thus, cardiac time interval experienced more dispersion once arousal occurred in compare to pre-arousal conditions. The average post-onset QT and RR intervals gradually dropped at arousal onset,

| | | | $Gr_{-4}$ | $Gr_{-3}$ | $Gr_{-2}$ | $Gr_{-1}$ | $Gr_0$ | $Gr_1$ | $Gr_2$ | $Gr_3$ | $Gr_4$ | $Gr_5$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Types | QT | p-Value | N.S | N.S | N.S | N.S | N.S | 0.001 | 0.08 | N.S | 0.03 | N.S |
| | | Post hoc Signs | – | – | – | – | – | SA vs RERA | – | – | SA vs MA | – |
| (MA, SA, RERA) | RR | p-Value | 0.03 | 0.0003 | <0.0001 | <0.0001 | <0.0001 | 0.25 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| | | Post hoc Signs | SA vs MA | SA vs MA | SA vs MA<br>SA vs RERA | SA vs MA<br>SA vs RERA | SA vs MA<br>SA vs RERA<br>MA vs RERA | – | SA vs MA<br>SA vs RERA<br>MA vs RERA | SA vs MA<br>SA vs RERA<br>MA vs RERA | SA vs MA<br>SA vs RERA<br>MA vs RERA | SA vs MA<br>SA vs RERA |
| Stages | QT | p-Value | 0.031 | N.S | N.S | 0.019 | 0.009 | <0.0001 | 0.029 | N.S | N.S | N.S |
| | | Post hoc Signs | – | – | – | – | N2 vs REM | N2 vs REM | – | – | – | – |
| (N1, N2, N3, REM, Wake) | RR | p-Value | N.S | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.019 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| | | Post hoc Signs | – | W vs REM<br>W vs N1<br>W vs N2 | W vs REM<br>W vs N1<br>W vs N2<br>N1 vs N3 | W vs REM<br>W vs N1<br>W vs N2<br>N3 vs N1<br>N3 vs N2<br>N3 vs REM | W vs REM<br>W vs N1<br>W vs N2<br>N3 vs N1<br>N3 vs N2<br>N3 vs REM | W vs N1<br>W vs N2 | W vs REM<br>W vs N1<br>W vs N2<br>N3 vs N1<br>N3 vs N2<br>N3 vs REM | W vs REM<br>W vs N1<br>W vs N2<br>N3 vs N1<br>N3 vs N2<br>N3 vs REM | W vs REM<br>W vs N1<br>W vs N2<br>N3 vs N1<br>N3 vs N2<br>N3 vs REM | W vs REM<br>W vs N1<br>W vs N2<br>N3 vs N1<br>N3 vs N2<br>N3 vs REM |
| Duration (STA, LTA) | QT | p-Value | 0.04 | N.S | N.S | N.S | N.S | <0.0001 | N.S | N.S | N.S | N.S |
| | RR | p-Value | N.S | 0.003 | 0.0001 | 0.005 | <0.0001 | 0.02 | 0.0001 | <0.0001 | <0.0001 | <0.0001 |

**Table 4.4:** Analysis of cardiac interval gradients variability with consideration of arousal type (MA, SA, RERA), duration (STA, LTA) and sleep stage. The **W**, **N1**, **N2**, **N3** and REM represent sleep stages of wake, non-rapid eye movement 1, 2, 3 stages and rapid eye movement. **N.S** refers to non statistically significant results.

| Features | Pre-Onset | | Post-Onset | | R | Paired t-test |
|---|---|---|---|---|---|---|
| | mean | SD | mean | SD | | (p-Value) |
| rangeRR (ms) | 32.44 | 22.12 | 38.2 | 19.98 | 0.441 | <0.0001 |
| rangeQT (ms) | 6.88 | 4.27 | 7.93 | 4.08 | 0.408 | <0.0001 |
| meanRR (ms) | 1047.03 | 133.29 | 1033.71 | 139.16 | 0.992 | <0.0001 |
| meanQT (ms) | 416.32 | 29.42 | 409.12 | 28.32 | 0.987 | <0.0001 |
| VarRR ($ms^2$) | 259.28 | 414.47 | 198.77 | 236.79 | 0.456 | <0.0001 |
| VarQT ($ms^2$) | 10.43 | 14.47 | 7.23 | 8.11 | 0.426 | <0.0001 |
| logVarRR ($ms^2$) | 2.02 | 1.35 | 2.06 | 0.44 | 0.176 | *N.S* |
| logVarQT ($ms^2$) | 0.736 | 0.566 | 0.658 | 0.675 | 0395 | <0.0001 |
| QTVi (n.u) | -1.13 | 3.13 | -1.40 | 1.74 | 0.197 | <0.0001 |
| *QT/RR Slope* (n.u) | 0.404 | 0.048 | 0.557 | 0.049 | 0.137 | <0.0001 |
| QT/RR $R^2$ (n.u) | 0.606 | 0.046 | 0.442 | 0.057 | 0.138 | <0.0001 |

**Table 4.5:** A comparison of cardiac statistical features 5 seconds before and 10 seconds after arousal onset. $R$ represents linear correlation coefficient between features before and after onset. $p-value$ indicates significant level. $SD$ and $n.u$ refer to the standard deviation and normalised units.

as the the pre-onset *meanRR* and *meanQT* were greater than the post-onset similar features. The linear correlation ratio between $Pre_{meanRR}$ and $Post_{meanRR}$ was 0.99 that indicate the change in RR interval can be modelled through a linear regression fit.

The variance of cardiac intervals, *VarRR* and *varQT* indicate the variability around *meanRR* and *meanQT*, respectively. As shown in Table **4.5** The average variance of both QT and RR reduced after arousal onset as the average pre-onset *varQT* and *varRR* were 30% greater than post-onset ($Pre_{VarQT} = 10.4 \pm 14.5$ vs $Post_{VarQT} = 7.2 \pm 8.1$ and $Pre_{VarRR} = 259.3 \pm 414.5$ vs $Post_{VarRR} = 198.8 \pm 236.8$). To investigate how variance changes over time, QT and RR time-series were divided into seven sub-vectors including $t_{-2}$, $t_{-1}$, $t_o$, $t_1$, $t_2$, $t_3$ and $t_4$ which represents cardiac intervals from [onset-5 to onset-4], [onset-3 to onset-2], [onset-1 to onset], [onset+1 to onset+2]; [onset+3 to onset+4], [Onset+5 to onset+6] and [onset+7 to onset+10], respectively. By this means, cardiac interval variance was monitored second-by-second. We also used logarithmic value to gain the normal distribution. Berger equation (*QTVi*) [156] was also computed to investigate the beat-to-beat QT variability pre- and post arousals. Based on the definition, *QTVi* is a measure of relative magnitude of QT interval changes compared to heart rate variability. Figure **4.10** depicted and compared QT and RR variability as well as *QTVi* before and after arousal

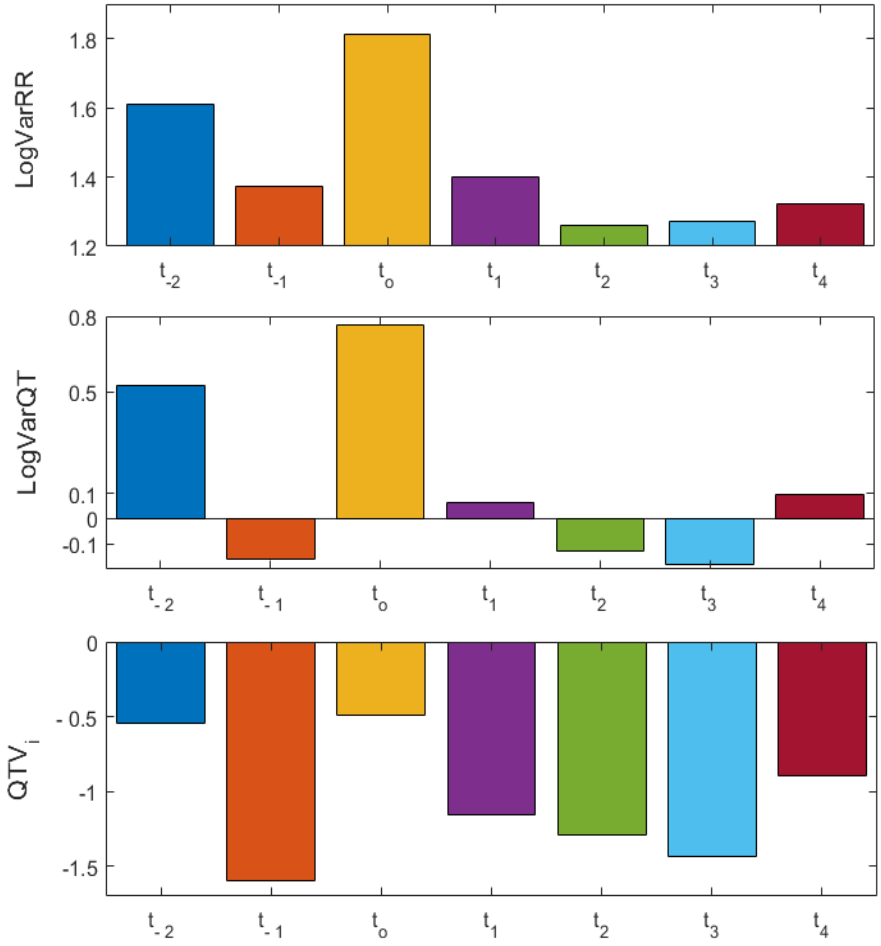



**Figure 4.10:** Barcharts demonstrate QT and RR interval variance fluctuations second-by-second. $t_{-2}$, $t_{-1}$, $t_o$, $t_1$, $t_2$, $t_3$ and $t_4$ represents cardiac intervals [onset-5 onset-4], [onset-3 onset-2], [onset-1 onset], [onset+1 onset+2], [onset+3 onset+4], [Onset+5 onset+6] and [onset+7 to onset+10], respectively. *logVarQT* and *logVarRR* also indicate the logarithm of variances of QT and RR

onset. The *logVarRR* as an indicator of RR variability reached to the maximum amount at onset and then significantly dropped and this reduction continued until 5 seconds after onset. Similarly, for QT interval, the highest degree of variability occurred at arousal onset and after that *logVarQT* started to decrease where it reached the minimum variability about 7 secs after arousal onset. *QTVi* marker was negative in both pre- and post-onset conditions, although it dropped by about 23% after arousal inducing. Similar to QT and RR variability, the *QTVi* reached the maximum at onset and then continuously reduced for several moments after arousal inducing.

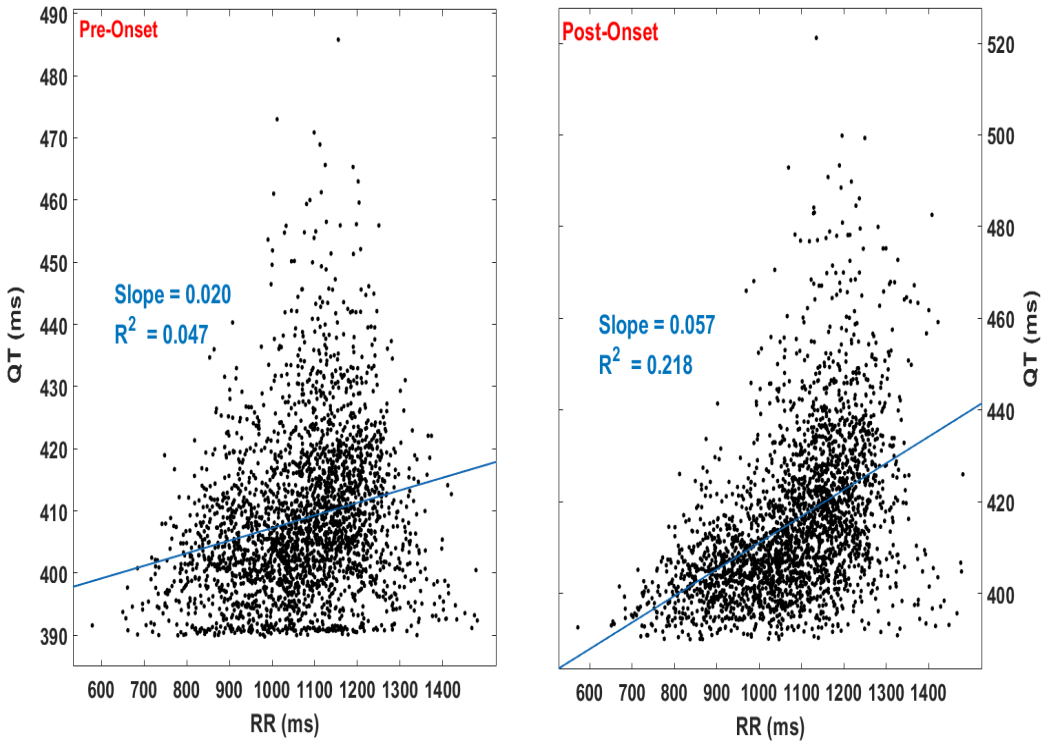



**Figure 4.11:** Graphical demonstration of curve linear regression for QT/RR relationship before (**Left**) and after (**Right**) arousal onset. The dependency of $RR/QT$ after arousal onset was four time stronger than pre-onset conditions.

#### 4.3.2.1 QT/RR linear regression model

We applied linear curve fitting analysis to find an empirical model for cardiac intervals changes. To differentiate *QT/RR* regression models at arousal onset, we designed two separate curve fittings. All subjects' average of RR and QT intervals 3 secs before arousal were utilised to describe pre-onset *QT/RR* dependency (Figure **4.11-Left**). On the other hand, the average cardiac intervals 3 secs post arousal were used to design curve fitting model of post-onset *QT/RR* dependency (Figure **4.11-Right**). Slope and $R^2$ are two main parameters of linear regression process. Slope represents the rate of change in regression model and indicated how much two datasets are depended, while $R^2$ measures how close the data are to the fitted regression line. Obtained results shows that the $R^2$ value after onset ($R^2 = 0.218$) was significantly greater than pre-onset regression ($R^2 = 0.047$). It means the *QT/RR* dependency can considerably increase once an arousal occurs. Moreover, we also estimated the *QT/RR slope* and $R^2$ subject by subject. The mean and standard deviation of $QT/RR\ Slope$ and $QT/RR\ R^2$ in normalised units were tabulated in Table **4.3** as well. The Pearson linear correlation of pre- and post-onset of these features were comparably small ($R_{Slope} = 0.137$

and $R_{R^2} = 0.138$) in contrast to other obtained ratios for other extracted features.

#### 4.3.2.2 Arousal Duration and Cardiac Intervals

Arousals were previously categorised into two groups short-term and long-term arousals. In each subject, arousals were divided into STA or LTA groups based on their duration and four matrices were generated including $QT_{STA}$, $QT_{LTA}$, $RR_{STA}$ and $RR_{LTA}$. All subjects had long duration arousals, then all had $RR_{LTA}$ and $QT_{LTA}$ whilst only one subject had no arousal episode shorter than 8 secs and consequently no $QT_{LTA}$ and $RR_{LTA}$ matrices. Then, we computed $PRSA_{RR}$ and $PRSA_{QT}$ curves for developed matrices. Statistical analysis were applied to investigate whether the duration of arousal is associated to simultaneous QT or RR variability. Thus, we compared features like range, mean, variance of cardiac intervals along with *QTVi* in both groups and then assessed by two sample t-test to find out obtained results were statistically significant (The significance level: $p = 0.01$). Our findings show that indicators of QT and RR variability like range and variance of STA group were significantly different from LTA group ($p < 0.0001$). The average *VarRR* and *VarQT* in STA episode were 23% and 51% greater than LTA events that indicate the greater variability of both RR and QT in arousal shorter than 8 secs in contrast to longer arousals. This manifest a inverse association between cardiac interval variability and the duration of arousal episode.

| Statistical | Short-term | | Long-term | | p-value |
|---|---|---|---|---|---|
| Features | Mean | SD | Mean | SD | |
| rangeRR (ms) | 54.25 | 40.09 | 48.71 | 34.19 | <0.0001 |
| rangeQT (ms) | 13.49 | 8.16 | 11.17 | 6.06 | <0.0001 |
| meanRR (ms) | 1036.5 | 135.86 | 1030.8 | 130.9 | N.S |
| meanQT (ms) | 415.85 | 34.22 | 416.16 | 33.19 | N.S |
| VarRR ($ms^2$) | 345.28 | 821.12 | 280.3 | 636.84 | 0.0013 |
| VarQT ($ms^2$) | 17.13 | 25.42 | 11.31 | 11.93 | <0.0001 |
| logVarRR ($ms^2$) | 2.18 | 0.56 | 2.09 | 0.54 | <0.0001 |
| logVarQT ($ms^2$) | 0.95 | 1.19 | 0.84 | 0.73 | <0.0001 |
| QTVi (n.u) | 0.91 | 0.04 | 0.92 | 0.03 | <0.0001 |

**Table 4.6:** Features comparison in short- and long-term arousals

#### 4.3.2.3 Arousal Types and Cardiac Intervals

Arousals were also classified to three different groups, movement arousals, respiratory effort related arousals and spontaneous arousals regarding to the association of arousal to physiological events. In each subject, all arousals were categorised into these three groups. There were SA episodes in all 2659 subjects, however in 48 participants, no MA event was scored (1.8%). Furthermore, in 13 out of 2659 participants (0.5%), we did not find any RERA events. $PRSA_{QT}$ and $PRSA_{RR}$ were estimated for each arousal category in each subject. In this case, for almost all subjects, we obtained three $PRSA_{QT}$ as well as three $PRSA_{RR}$ represented cardiac intervals fluctuations in MA, RERA and SA events. In order to compare cardiac intervals dependency in different arousal types before and after arousal onset, we applied linear curve fitting for each arousal type as well. Figure **4.12** depicts QT/RR curve fitting of MA, RERA and SA patterns. The QT/RR dependency after arousal inducing is considerably increasing regardless of arousal types. Our findings also show the spontaneous arousals leads to greatest QT and RR dependency ($R^2 = 0.198$) in comparison with movement and respiratory arousals.

The statistical cardiac parameters were computed to analyse the variability of QT and RR intervals in different types of arousals. Table **4.7** presents a comparison of mean and standard deviation of features in three arousal groups. One-way ANOVA test also assessed whether extracted features significantly differed in various arousal types or not (significance level: $p = 0.05$). Our observations show that range and variance of RR interval (*rangeRR* and *logVarRR*) were greater in MA and RERA episodes than spontaneous arousals. It can be interpreted that MA and RERA which are accompanied with a pathological event can lead to more dispersion in RR interval than SA episodes. Similarly, both *rangeQT* and *logVarQT* were comparably greater in MA and RERA groups than SA group.

The ANOVA test rejected any significant difference of some features in different types of arousals (Table **4.7**). Both *meanQT* and *meanRR* were altered after onset in all types of arousals, however their changes was not associated to the type of arousal. The obtained p-value rejected the hypothesis that means of cardiac intervals are depended to arousal type. We observed the similar situations in other features like $QT/RR$ Slope and $QT/RR$ Residual. The obtained p-value in this case confirmed that the variability in QT and RR linear correlation and strength during arousal inducing are independent of any pathological events that accompanied arousals. The difference between both *rangeQT* and *rangeRR* in arousal

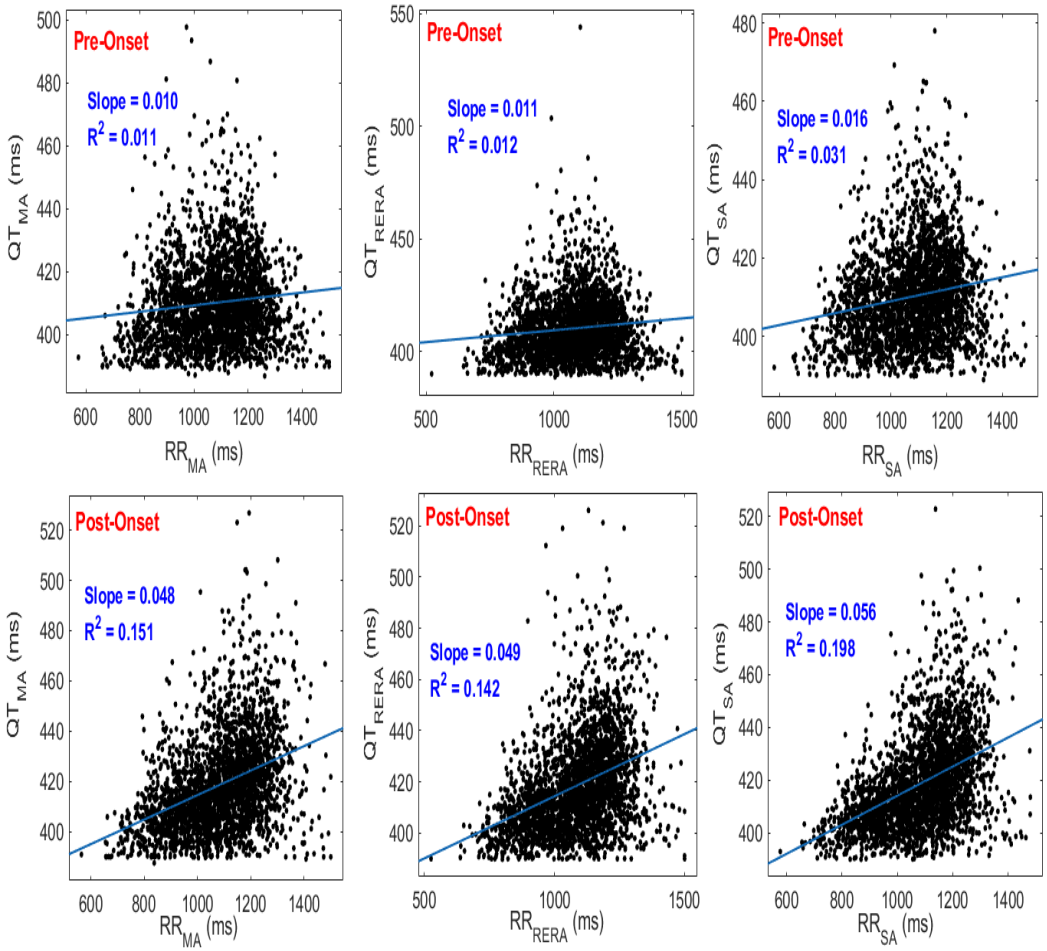



**Figure 4.12:** Curve fitting of QT/RR interval relationship in various arousal types pre- (**Top**) and post-onset (**bottom**).

groups was significant. The post hoc Tokey's honest significance test also revealed that the range of cardiac intervals is depended to arousal type and correspondingly to physiological event that cause the arousal. The variances of QT and RR intervals (*VarQT* and *VarRR*) were also assessed through ANOVA test for different types of arousals. We found a significant difference in variance of RR in various arousal groups ($p < 0.0001$). The post hoc test of *VarQT* indicates that variance of spontaneous arousals was significantly different from respiratory and movement arousals. However, *VarQT* difference between RERA and MA was not statistically significant.

Both variance and range are markers of interval variability. They reveal how data varies around of mean. Figure **4.13** visualised the mean comparison of range and variance of QT and RR in various arousal types. The average *rangeQT* and *VarQT* in spontaneous arousal was considerably smaller than movement and respiratory arousals. In terms of vari-

| Features | MA | | RERA | | SA | | ANOVA | Post hoc Signs |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | | |
| rangeRR (ms) | 65.5 | 58.2 | 60.1 | 49.6 | 47.4 | 30.4 | <0.0001 | MA vs SA<br>RERA vs SA<br>MA vs RERA |
| rangeQT (ms) | 30.3 | 19.4 | 29.1 | 17.9 | 24.9 | 13.1 | <0.0001 | MA vs SA<br>RERA vs SA<br>MA vs RERA |
| meanRR (ms) | 1081.3 | 147.8 | 1083.3 | 146.1 | 1083.4 | 141.4 | N.S | – |
| meanQT (ms) | 416.5 | 18.6 | 416.5 | 18.8 | 416.7 | 17.5 | N.S | – |
| logVarRR ($ms^2$) | 2.68 | 1.179 | 2.62 | 0.99 | 2.47 | 0.83 | <0.0001 | MA vs SA<br>RERA vs SA |
| logVarQT ($ms^2$) | 2.07 | 0.79 | 2.04 | 0.82 | 1.95 | 0.68 | <0.0001 | MA vs SA<br>RERA vs SA |
| QTVi (n.u) | 0.68 | 0.12 | 0.73 | 0.11 | 0.83 | 0.13 | 0.08 | – |
| $QT/RR$ Slope (n.u) | 0.565 | 0.03 | 0.566 | 0.02 | 0.565 | 0.02 | N.S | – |
| $QT/RR$ $R^2$ (n.u) | 0.434 | 0.05 | 0.434 | 0.04 | 0.435 | 0.05 | N.S | – |

**Table 4.7:** A comparison of features in various arousal groups. Post hoc sings MA, RERA and SA refer to movement, respiratory and spontaneous arousal group.

ability of RR interval, our findings show that the variance and range of cardiac intervals in MA and RERA were significantly greater than SA. The MA events even caused RR interval more variable in compare to RERA episodes. These observations show that arousals associated with respiratory or movement episodes influence cardiac intervals stronger than spontaneous arousals.

#### 4.3.2.4 Sleep stages and Cardiac Intervals

To study the effect of sleep stage and cardiac interval fluctuations during sleep events, each subject's scored arousals were categorised into five group based on the sleep stage that arousal ended. For each arousal group and in each subject, we applied PRSA algorithm and developed $PRSA_{RR}$ and $PRSA_{QT}$ curves. For instance, if a subjects had arousals in stage $NREM1$, $NREM2$ and $REM$, three $PRSA_{QT}$ and three $PRSA_{RR}$ were generated. Out of 2659 subjects that we analysed, 2629 subjects had at least one arousal episode which terminated at stage NREM1 (98.8%). This rate (percentage) for NREM2, NREM3, REM and wake stage were 2659 (100%), 1867 (70.1%), 2625 (98.7%) and 2637 (99.2%), respectively. Statistical analysis allowed to investigate the association sleep stage and RR and QT variability during the arousal occurrence. ANOVA test also assessed the statistical significance of obtained results. Our findings show that features like range and variance which are indicators of

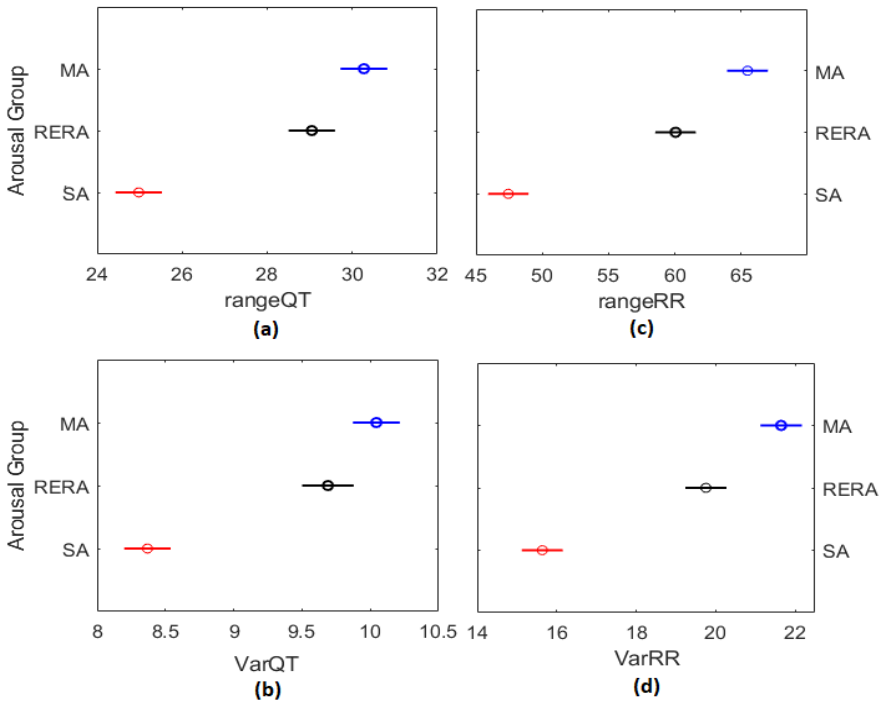



**Figure 4.13:** Means comparison of range and variance of cardiac intervals in different arousal types using post hoc test

cardiac interval variability significantly differed during arousals in different sleep stages ($p < 0.0001$). This demonstrates the role of sleep stage in QT/RR fluctuations. While the the average QT and RR (*meanQT* and *meanRR*) did not significantly change during different sleep stages, QT and RR variability were associated to sleep stages. *Slope* and $R^2$ as two marker of dependency between QT and RR also changed in different sleep stages. The stage of NREM1 had the highest average normalised $QT/RR$ slope (0.79) that indicates the highest QT/RR dependency. Arousals in NREM1 category also had the lowest $R^2$ as a goodness of fit parameter.

#### 4.3.2.5 Cardiac Intervals and Arousal indices

In this study, five arousal indices were derived from number of different sleep events and total sleeping time. *RDI* and *AI* are two known sleep marker which determine the severity of sleep disordered breathing (SDB) and the degree of sleep fragmentation. Beyond these two indices, we also defined three more indices (*MAI*, *RAI* and *SAI*) based upon the number of MA, RERA and SA in one hour of sleeping time. These measures reflect different dimensions of subjects' sleep quality. For each subject, we calculated all five indices to

| Features | NREM1 $n$ = 2629 | | NREM2 $n$ = 2659 | | NREM3 $n$ = 1867 | | REM $n$ = 2625 | | Wake $n$ = 2637 | | ANOVA | Post hoc Signs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | mean | SD | mean | SD | mean | SD | mean | SD | mean | SD | | |
| rangeRR | 81.36 | 73.64 | 48.56 | 36.16 | 159.13 | 171.7 | 82.94 | 69.28 | 101.62 | 78.96 | <0.0001 | W vs N1, N2, N3, R<br>N1 vs N2, N3<br>N2 vs N3, R<br>N3 vs R |
| rangeQT | 23.28 | 19.38 | 11.33 | 6.96 | 45.79 | 40.09 | 21.68 | 15.57 | 27.36 | 18.41 | <0.0001 | W vs N1, N2, N3, R<br>N1 vs N2, N3<br>N2 vs N3, R<br>N3 vs R |
| meanRR | 1036.23 | 140.87 | 1034.27 | 133.51 | 1030.88 | 156.21 | 1027.68 | 134.76 | 1028.22 | 133.46 | N.S | – |
| meanQT | 415.26 | 36.35 | 415.92 | 33.71 | 417.52 | 39.08 | 416.45 | 34.52 | 416.44 | 34.31 | N.S | – |
| LogVarRR | 2.44 | 0.68 | 2.08 | 0.56 | 2.98 | 0.85 | 2.51 | 0.6 | 2.67 | 0.99 | <0.0001 | W vs N1, N2, N3, R<br>N1 vs N2, N3, R<br>N2 vs N3, R<br>N3 vs R |
| LogVarQT | 1.32 | 1.48 | 0.79 | 1.09 | 1.82 | 1.81 | 1.3 | 1.55 | 1.52 | 1.45 | <0.0001 | W vs N1, N2, N3, R<br>N1 vs N2, N3<br>N2 vs N3, R<br>N3 vs R |
| QTVi | -0.64 | 3.62 | -1.01 | 2.8 | -0.71 | 4.06 | -0.85 | 3.72 | -0.68 | 3.74 | 0.001 | N2 vs W, N1 |
| $QT/RR$ Slope | 0.79 | 0.02 | 0.28 | 0.02 | 0.45 | 0.03 | 0.17 | 0.02 | 0.58 | 0.02 | <0.0001 | W vs N1, N2, N3, R<br>N1 vs N2, N3, R<br>N2 vs N3, R<br>N3 vs R |
| $QT/RR$ $R^2$ | 0.18 | 0.02 | 0.72 | 0.02 | 0.51 | 0.03 | 0.77 | 0.03 | 0.42 | 0.02 | <0.0001 | W vs N1, N2, N3, R<br>N1 vs N2, N3, R<br>N2 vs N3, R<br>N3 vs R |

**Table 4.8:** Sleep stage effect on QT and RR variability during sleep arousals. The number of subjects who had arousals ended at a particular sleep stage is referred by $\boldsymbol{n}$. Post hoc signs: *N1*, *N2*, *N3*, *R* and *W* represents sleep stage of NREM1, NREM2, NREM3, REM and Wake, respectively. Normalised units were used for $QTVi$, $QT/RR\ Slope$ and $R^2$ features.

investigate on the association of cardiac intervals change and different sleep markers. To compare and tabulate cardiac variability, we calculated the variance of QT and RR, as a measure of variability, in each subjects' arousal group. The linear correlation coefficient ($R$) of the variance of QT and RR interval with arousal indices plus $p$-value were evaluated and illustrated in Table **4.5**. To gain a normal distribution, we used the log-transformed equivalent of each arousal index as well as QT and RR variance. The obtained results show a negative correlation between interval variance and arousal index.

In case of movement arousal (MA), the correlation coefficient (R) of $VarQT$ and $log(MAI)$ was -0.317, whist $R = -0.272$ was the linear correlation of $VarRR$ and $MAI$. We computed the R in respiratory and spontaneous arousals as well as the cardiac variance of subjects' all arousals, regardless of their type. However, the resulting R and signifi-

cance level indicates lack of any considerable correlation between *MAI* and cardiac interval variance in RERA, SA episodes. In fact, only *VarQT* and *VarRR* had a meaningful and significant correlation with MAI. It indicates the variability of cardiac intervals during MA episodes is associated with the number of occurred movement arousals and consequently with the number of periodic or non-periodic limb movement events.

| | | | MAI | RAI | SAI | AI | RDI |
|---|---|---|---|---|---|---|---|
| MA | VarQT | R | **-0.317** | -0.023 | -0.023 | **-0.097** | -0.009 |
| | | p | <**0.0001** | N.S | 0.N.S | <**0.0001** | N.S |
| | VarRR | R | **-0.272** | -0.005 | -0.005 | -0.083 | 0.010 |
| | | p | <**0.0001** | N.S | N.S | <0.0001 | N.S |
| RERA | VarQT | R | -0.035 | **-0.292** | -0.090 | **-0.184** | **-0.251** |
| | | p | 0.071 | <**0.0001** | <0.0001 | <**0.0001** | <**0.0001** |
| | VarRR | R | -0.017 | **-0.287** | -0.088 | **-0.204** | **-0.265** |
| | | p | N.S | <**0.0001** | <0.0001 | <**0.0001** | <**0.0001** |
| SA | VarQT | R | -0.005 | -0.023 | **-0.125** | -0.059 | -0.025 |
| | | p | N.S | N.S | <**0.0001** | 0.0004 | N.S |
| | VarRR | R | 0.015 | -0.023 | **-0.121** | -0.076 | -0.022 |
| | | p | N.S | N.S | <**0.0001** | <0.0001 | N.S |
| All | VarQT | R | -0.047 | 0.089 | **-0.126** | **-0.139** | 0.069 |
| | | p | 0.016 | <0.0001 | <**0.0001** | <**0.0001** | 0.0004 |
| | VarRR | R | -0.010 | -0.036 | -0.051 | -0.065 | -0.042 |
| | | p | N.S | 0.071 | 0.009 | 0.001 | 0.042 |

**Table 4.9:** A comparison of linear correlation of cardiac intervals variability and arousal indices. In order to reach normal distribution, features and indices were log-transformed. $R$ in each case represents Pearson correlation coefficient and $p$ indicates significance level.

In terms of respiratory arousal index, similar outcome was obtained. The number of RERA events was negatively correlated with the post-onset QT and RR variability in RERAs ($R_{VarQT}$ = -0.292 & $R_{VarRR}$ = -0.287 ). We did not observe any correlations between RAI and variances in other types of arousals. We also investigated whether cardiac interval variability in different types of arousal are associated with sleep fragmentation. Our findings shows a correlation between intervals variability and *AI* ($R_{VarQT}$ = -0.184 and $R_{VarRR}$ = -0.204), nevertheless this correlation was halved in other types of arousal. This manifest that cardiac fluctuations generated by RERA events are more susceptible to make sleep fragmented and deprived than spontaneous arousals.

*RDI* is the indicator of sleep apnoea diseases. The higher *RDI*, the severer SDB conditions. The variability of both QT and RR intervals with RDI only in RERA arousal was significant ($R_{VarQT}$ = -0.251 & $R_{VarRR}$ = -0.265). Hence the variability of QT and RR during respiratory arousals are reversely correlated with the *RDI* as well as the severity of SDB.

### 4.3.3 QT and RR inter-relations during Arousals

We employed bivariate phase rectified signal averaging (BPRSA) algorithm to investigate about the cardiac intervals inter-relations. The aim was to find out how increase or decrease of QT before and after onset influence on RR interval and vice versa. Thus, we defined four BPRSA curves to cover all changes 5 secs prior to onset and 5 secs following of it ($k = onset-5, onset-4, ..., onset, ..., onset+5$). The $BPRSA_{QT\rightarrow RR}\nearrow$ curve indicated the RR changes triggered by QT increase, whilst $BPRSA_{QT\rightarrow RR}\searrow$ represented the RR changes by QT decrease. Similarly, $BPRSA_{RR\rightarrow QT}\nearrow$ and $BPRSA_{RR\rightarrow QT}\searrow$ were defined to analyse how RR increase or decrease could change QT. In each curve and at each particular moment, e.g. arousal onset or 1 second after or before it, we computed the slope. Whether the slope was positive or negative could determine that the curve was increasing or decreasing at that particular point.

We assumed that QT and RR changes were in same direction. In other words, an increase in QT, would trigger RR to shift and decrease in QT results RR reduction. On the other hand, any RR rise or fall was assumed to develop a shift or drop in QT, respectively. To investigate the mutual effect of cardiac intervals on each other, we computed the percentage of subjects whose QT and RR changes were in same direction and was in accordance with our initial assumption (Figure **4.14**). Hence, the higher percentage indicates that in more subjects cardiac changes occurred in same direction. According to obtained results, from 5 to 3 secs pre-onset ($k=-5$ to $-3$), QT increase triggered about 30% of subjects RR to increase ($QT\rightarrow RR\nearrow$), whereas QT reduction resulted RR drop ($QT\rightarrow RR\searrow$) in about 70% of subjects. Vice, versa, one second before onset ($k=-1$), in more than 70% of subjects, QT increase led to RR increase, whilst QT drop caused RR drop in 34% of subjects. On the other hand, pre-onset ($k=-5,-4,...,-1$) RR increase caused QT elevation ($RR\rightarrow QT\nearrow$) in about half of subjects. This means RR pre-onset upward trend does not necessarily lead to QT increasing. Furthermore, RR pre-arousal shortening caused QT shortening ($RR\rightarrow QT\nearrow$) in about half of arousals.

The pre-onset conditions can be interpreted as 'no arousal period' where the cardiac

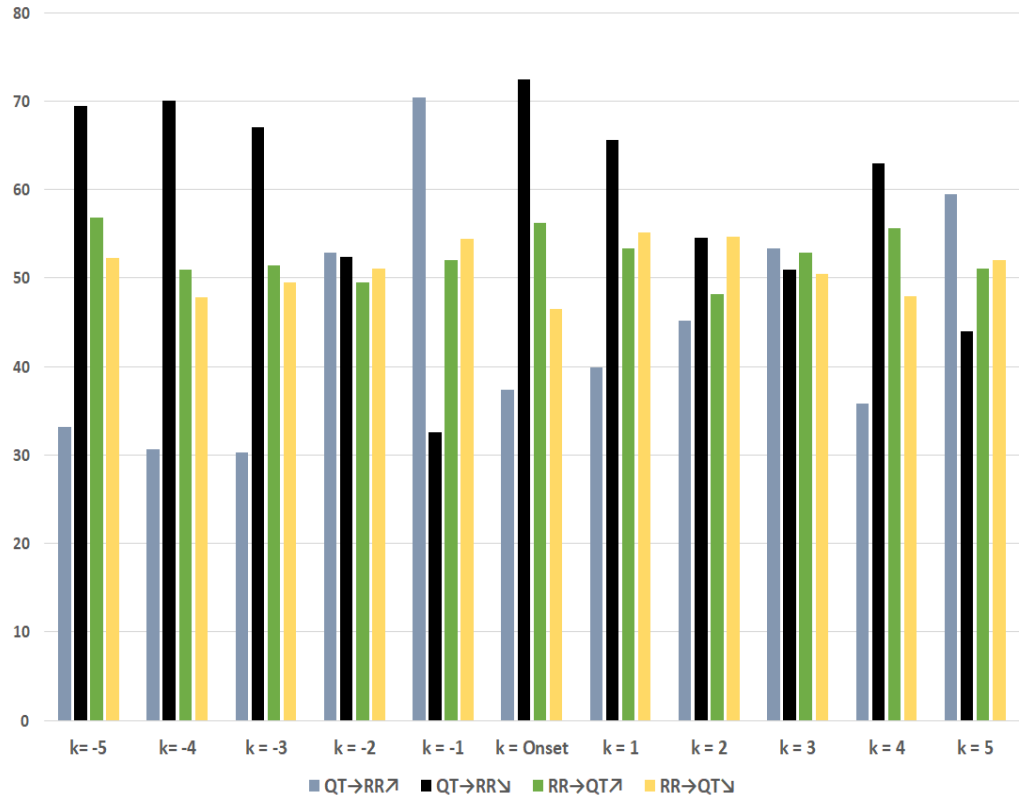



**Figure 4.14:** Bivariate PRSA analysis of cardiac intervals. $BPRSA_{QT\rightarrow RR}$ and $BPRSA_{RR\rightarrow QT}$ were developed to investigate QT and RR inter-relations during arousal occurrence. For instance, $QT \rightarrow RR \nearrow (\%)$ indicates the percentage of subjects whose $BPRSA_{QT\rightarrow RR}$ curve increased at a particular time ($k$) once $QT$ increased. Similarly, $QT \rightarrow RR \searrow (\%)$ demonstrates QT drop in what percentage of subjects led to RR drop at $k$.

fluctuations are not depended to any arousal intervention, but might be related to the post-arousal physiological activation such as SDB even or limb movement episodes. On the other hand, the post-onset changes indicate the influence of sleep arousals and adjacent physiologic events on cardiovascular mechanism. Sleep arousal like a simulator may trigger autonomic nervous system and affect on cardiovascular parameters. At onset ( $k = Onset$), QT shortening mainly triggered RR to decrease ($\approx 74\%$), whilst QT prolongation was also likelier to result RR shortening (62%). Furthermore, RR increase at onset would be accompanied with QT shifting by 56%. The QT probability of changes caused by RR increase ($RR \rightarrow QT \nearrow$) or decrease ($RR \rightarrow QT \nearrow$) was about 50%. This shows any changes in RR during arousal occurrence has approximately the same chance to cause a shift or drop in QT. Contrarily, any QT alterations are more likely to lead RR shortening except one second before onset ($k = -1$).

## 4.4 Discussion

The cardiac intervals fluctuations during sleep arousal occurrence was broadly studied in this chapter. We analysed a very large database consisting of 2659 PSG recordings and we faced some limitations such as artefacts, noises and missing data. In fact, our analysis should consider those issues and find a solution to eliminate artefacts, minimise noises and neutralise missing data effects. The PRSA analysis allowed to generate a precise averaging equivalent for all arousal activation of a subject. By development of cardiac interval gradients, the effect of arousal in instantaneous fluctuations of cardiovascular dynamics was investigated.

Analysis of $PRSA_{QT}$ gradients demonstrates that QT had a downward trend in about 39% of subjects at least 4 seconds before ($Gr_{-4}$) arousal onset (Figure **4.9**). One second later ($Gr_{-3}$), the probability of QT reduction was about 63%. Right before, arousal onset the probability of $PRSA_{QT}$ decrease was about 65%. This manifests a continuous QT shortening during moments pre- and post-onset. Similarly, pre-arousal RR drop was observed in more than 70% of subject until 2 seconds before onset (Figure **4.8**). In addition, $PRSA_{RR}$ interval shortened by at least 20 ms in more than a quarter of subjects ($n = 691$). The gradient analysis of cardiac time intervals demonstrates a significant QT and RR shortening during arousal which is in agreement with previous studies [91, 74]. Post arousal QT and RR shortening also indicate the effect of arousals on cardiovascular mechanism. In other words, arousal occurrence causes cardiac time intervals, which are representing the cardiac function, be affected. The effect of arousal on cardiac function vary in different arousal types. Our finding show the effect of RERA episodes was more prominent than other arousal types. This can be interpreted that SDB events that induced arousal, they also triggered cardiovascular system and cause caridac interval fluctuations.

QT variability represents changes in the ventricular depolarisation period and along side with RR which is indicator of heart period provides indexes of the autonomic regulation at the sinus node and ventricular levels [157]. The amount of QT variability can be considered as an indirect measure of the ventricular sympathetic control if it progressively increases as a function of the sympathetic drive and this augmentation is accompanied by the rise of the amount of QT variability unrelated to RR changes and respiratory-related fluctuations [157]. An arousal episode like a trigger cause a sympathetic surge which can be reflected as sudden alterations on QT modulation.

The duration of a transient arousal can influence on the post-arousal heart rate responses [158, 126, 159]. In terms of the effect of the duration on cardiovascular dynamics, our observations show that RR momentary interval fluctuations are depended to the duration of arousals (Table **4.4**). RR gradients from 3 seconds prior to arousal ($Gr_{-3}$) to at lease 5 seconds after onset ($Gr_5$) in short- and long-term arousal were significantly different ($p < 0.0001$), the QT interval instantaneous changes did not significantly differ between two arousal categories. The association of RR intervals to the duration of arousal is in agreement with Trinder *et al.* that the characteristics of post-arousal HR like magnitude and duration may significantly differ by arousal duration. According to literature, the increase in HR is strongly correlated with arousal duration [126] and our findings show that RR and QT variability are reversely associated with arousal duration ($p < 0.001$).

QT intervals seem to be more variable in movement and respiratory arousals than spontaneous episodes where both *LogvarQT* and *rangeQT* in MA and RERA were greater than SA patterns (Figure **4.13**). Even the range of QT in MA and RERA episodes was wider than SA by about 20%. Similarly, *rangeRR* and *LogvarRR* results indicate that the RR variability of movement and respiratory arousals was significantly greater than spontaneous arousals. Smith *et al.* found that RR shortening during respiratory arousal are greater than SA episode [74], while obtained results show that both RR and QT had a greater variability in RERA in compare with SA. Both MA and RERA are highly depended to body movement and respiratory episodes which occurred and terminated before arousal inducing, while SA episode is not related to any of those pathological events. Consequently, once each of these events occurs, a sudden change in cardiac cycle is expected. SDB events like partial or full blockage of airway can temporarily disturb the cardiovascular mechanism and this may appear as QT and RR fluctuations. At the same time, they may stimulate autonomic system and induce sleep arousal. Similarly, high RR and QT variability prior to MA, manifests that limb movement events are capable to trigger cardiovascular system. A comparison of HRV spectral components, previously, demonstrated that the $LF/HF$ ratio in PLM events are significantly stronger than non-movement episodes [160]. Hence, limb movement is associated with HRV and consequently with RR interval variability.

In chapter 2, HRV spectral components were shown as adequate markers for sleep staging. This manifest the impact of sleep stage on HRV as well as cardiac interval variability. The effect of sleep stages in cardiovascular activation during different pathological

events have been discussed in several studies [94, 161, 162, 163, 164]. Our findings shows that RR gradient variability during sleep arousal is associated with sleep stages, where the difference between wake stage with REM, NREM1 and NREM2 was statistically significant in majority of $Gr_i$ in either pre- or post-onset ($p < 0.0001$). On the other hand, QT gradients were significantly different only in NRME2 and REM groups at arousal onset. Hence, QT arousal-related momentary changes was independent of sleep stage. We also observed a significant association between sleep stages and RR variability which was in agreement with previous studies [94, 162]. QT variability unlike QT gradient, had a significant association with sleep stages ($p < 0.0001$). There are contradictory opinions about the association of QT variability and sleep staging. One study did not conclude any significant difference in QT variability in various sleep stages [94], whilst another manuscript found an association between QT variability during OSA events and sleep stages in only male subjects, but not female subject [164]. This study only focused on male subjects and we found an association between their QT variability during sleep arousals and sleep stages. Further analysis e.g. a similar study on female subjects could be helpful to reach a conclusive outcome about the sleep stage effect on QT variability.

RR interval is an equivalent term for HRV and as a result *VarRR* and *rangeRR* are both related to HRV. However, the QT variability refer to the variability in the autonomic neural outflow to the ventricular myocardium and is independent of HR [94]. RR-QT linear regression results show their correlation before arousal occurrence was very small ($R^2 = 0.04$) regardless of the types of upcoming arousals, whilst their correlation increased after arousal onset ($R^2 = 0.21$). This manifests stronger QT and RR association after arousal induces. An arousal episode as a sympathetic activation was expected to accompany with a decrease in QT/RR association, however we observed an improvement in QT/RR strength. This might be related to vagal rebound [165, 166]. According to the literature, vagal rebound may be involved in mechanisms resetting the baroreflex sensitivity at the onset and offset of stress [167].

The study also presented new analysis about the correlation of cardiac variability and the number of scored arousals in each subjects (Table **4.5**). The movement, respiratory and spontaneous arousal indices (MAI, RAI and SAI) as three measure of arousal frequency in one hour sleeping had negative correlation with QT and RR variability. The more frequent arousals resulted less variable QT and RR curves. The higher number of arousal makes

the sample size of PRSA analysis larger and consequently the variance decreases. Thus, the variability of $PRSA_{QT}$ and $PRSA_{RR}$ reversely affected with the number of arousals were used for signal averaging. Number of arousal can be used to quantify sleep fragmentation or can be added to respiratory events index and determines *RDI* as the main indicator of OSA severity. For calculation of AI, all arousals regardless of their types is usually considered [19]. In majority of subjects, the number of SA episodes was greater than RERA events, even in 58% of subjects SA index was twice of RERA index. It is expected that the impact of SA in sleep fragmentation was higher than RERA. However, the correlation of QT and RR variability with AI in RERA was about three times of SA. This demonstrates the prominent role of RERA in sleep fragmentation. Moreover, *RDI* is significantly associated with cardiac intervals variability. Our findings show QT and RR variability has a same influence in RDI and consequently in severity of sleep apnoea ($R = -0.265$ vs $R = -0.251$), despite they are independent. Another study has previously shown that *RDI* is more correlated with $QTV_i$ than HRV [94]. This shows the significant association cardiac interval variability with the degree of sleep apnoea. QT variability is more under sympathetic control while the magnitude of RR variability is more under vagal control. Thus, QT and RR variability after SDB events is expected not to be in same direction. The negative relation of RDI with both QT and HP variability is therefore, controversial. This may be related to influence of physiological artefacts affecting QT interval measurement such as cardiac axis movements related to respiration [168, 169]. The electrode movement attendant to respiration will distort the vector analysis of the heart's electrical potentials, nevertheless the greatest effect of respiratory on displacement of electrical axes was reported during deep inspiration stress or exercise [169], but not during sleep.

PRSA analysis could produce an average pattern of cardiac intervals activation of a subject. It also allowed to compare QT and RR variability and gradients in different subjects. However, it does not seem to be an adequate approach for arousal by arousal analysis. The gradient analysis of arousals (Table **4.2** and **4.3**) delivered a different outcome in contrast to PRSA gradient analysis.

Besides the known markers of autonomic activation such as heart rate, blood pressure and respiratory rate, new approaches have been suggested to analyse cardio-respiratory interactions. The squared coherence between QT and RR [165] and cardiopulmonary coupling [170] have provided new indices which can improve future studies of autonomic sys-

tem. The analysis of QT-RR squared coherence during sleep, particularly pre- and post-arousal occurrence in men and women cohorts can be considered in prospective studies.

The frequency of arousals is often used to quantify the level of sleep fragmentation [171] and associated with poor sleep quality [15] and daytime sleepiness in patients suffering from severe OSA [172]. Furthermore, frequent arousals are linked to increased emotional and physical fatigue in OSA sufferers [173]. Morover, patients with numerous arousals have more prevalent cardiovascular disease, arrhythmias and mortality [174] due to direct arousal-related conditions, involving activation of the autonomic nervous system, impairment of the circadian rhythm due to sleep fragmentation, nocturnal blood pressure and heart rate rises [91, 175, 176]. QT and RR cardiac interval allow to monitor cardiovascular function during sleep. The variability of intervals before and after sleep events can help to study the effect of different pathological sleep events on cardiovascular system. The sudden post-arousal QT and RR variability can be utilised as an effective marker for detection of sleep arousals and quantification of sleep fragmentation and prediction daytime sleepiness in clinical settings. Only one ECG channel recording is required for QT and RR estimation and it can be considered for simple sleep screening. The suggested method for development of cardiac interval gradients can be improved and and implemented for real-time cardiac function monitoring.

## 4.5 Conclusion

In this chapter the cardiac time interval modulations during sleep arousals were studied. The occurrence of an arousal episode is associated with increase in QT and RR interval variability which is related with arousal characteristics such type, duration and sleep stage. Cardiac interval gradients could determine instantaneous changes in QT and RR intervals. RR gradients are strongly depended to arousal type, duration and sleep stage, however QT-related arousal gradients were not necessarily associated to arousal characteristics. Both QT and RR interval variability are reversely associated with RDI and can determine the severity of obstructive sleep apnoea. BPRSA analysis could explain QT and RR inter-relations where any pre-arousal QT change (increase or decrease) is likelier to result RR shortening.

# Chapter 5

# Arousal Related Cardiac Interval Variability in Cardiovascular Disease

## 5.1 Background

Obstructive sleep events can have adverse effects on the cardiovascular system, including blood gas disturbances, large negative intrathoracic pressure changes, surges in sympathetic neural activity, alterations in heart rate, and surges in arterial blood pressure [94]. Patients suffering from severe sleep apnoea are more susceptible to develop coronary artery disease [177], congestive heart failure [178] and stroke. In other words, numerous arousals occurring in OSA sufferers likely contribute to the development of accompanying cardiac pathology [91]. As a consequence, patients with OSA disorder have higher cardiovascular mortality. The risk of heart failure, stroke and coronary heart disease rises in OSA patients [179]. OSA increases the risk of heart failure by 140% or risk of stroke by 60% [178]. In addition, patients with OSA have a higher recurrence of AF after cardio-version than non-OSA subjects [180]. Kanagla *et al.* observations also indicated that in OSA patients who did properly CPAP treatment, AF recurrence reduced in compare to patients did not.

Sudden cardiac death (SCD) is defined as unexpected, non-traumatic death occurring within 1 hour of the onset of new or worsening symptoms (witnessed arrest) or, if unwitnessed, within 24 hours of last being seen alive [181]. It is estimated that SCD annually causes over 300,000 deaths in the United States [182]. Obstructive sleep apnoea has been speculated as a risk factor of SCD. Gami *et al.* conducted a cohort study of 10,701 to investigate on the association of OSA ans SCD. Their findings demonstrated that the risk of incident SCD after an average of 5 years was significantly and independently associated

with OSA, based both on the frequency of apnoeas and hypopnoeas, and the severity of nocturnal oxygen desaturations [183]. Cardiac arrhythmias, stroke/ruptured cerebral aneurysm and myocardial infarction (MI) can potentially increase the probability of SCD [74]. OSA events are mainly accompanied with sleep arousals. In chapter 4, we demonstrated that sleep arousals can significantly trigger cardiovascular system changes. In addition, QT and RR time intervals are both likely to shorten right after arousal onset [74].

In this chapter, we focused on cardiac intervals variability during arousal to investigate whether QT and RR fluctuation at arousal onset are associated with patients physical and cardiovascular conditions. At the next step, the prognostic value of cardiac intervals variability for cardiovascular mortality was evaluated.

## 5.2 Methodology

### 5.2.1 Study Population

We conducted our research based upon MrOS cohort sleep study database. As mentioned in Chapter 4, all studied participants in MrOS study were male older than 65 years old. We could only choose subjects whose PSG data were adequate and their sleep scoring contains sufficient number of arousals. Thus, 2659 participants PSG dataset could meet our requirements. All participants were required to attend at a clinical interview and complete an enrolment form which contains questions about their medical history in advance of overnight PSG recordings. The participants' history of physician diagnosis of diabetes, hypertension, myocardium infarction (MI), transient ischaemic attack (TIA), congestive heart failure (CHF), stroke and chronic obstructive pulmonary disease (COPD) and etc were obtained in the questionnaire. In addition, participants were asked about their smoking habits and their height and weight were measured to compute body mass index (BMI). Furthermore, the questionnaire surveyed participants' physical activity through computation of physical activity scale for the elderly (PASE) score.

Participants were being followed up every four months to survey for new symptoms of CVD or clinically relevant arrhythmia. A board-certified cardiologist then verified all gathered documents using a pre-specified adjudication protocol [184].

### 5.2.2 Data preparation

The method for data preparation was exactly as same as in the previous chapter. Participants ECG and EEG recordings were being analysed to compute QT and RR intervals for each single arousal. In order to the arousal effect on QT and RR intervals, in each arousal 5 seconds prior to arousal onset and 10 seconds after that were picked. By this means, we could investigate cardiac intervals modulations moments before onset to find how arousal was induced and moments after onsets to monitor how arousal caused sudden changes in cardiovascular function. Hence, two cardiac arousal matrices were developed for all subjects. Each row of matrix, represented cardiac interval of each single arousal and contained RR and QT time series moments before and after arousal onset. Through phase rectified averaging signal algorithm, the $PRSA_{QT}$ and $PRSA_{RR}$ curves were estimated for each subject.

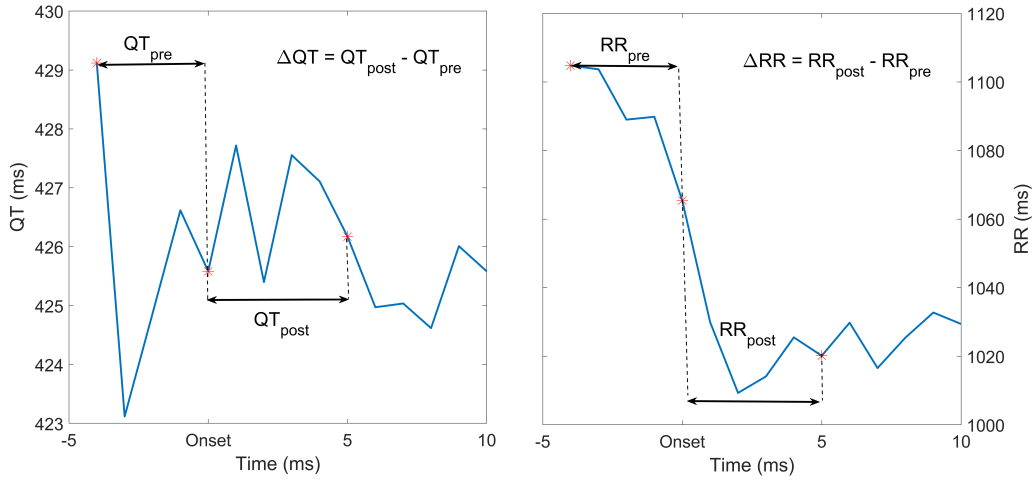



**Figure 5.1:** A graphical demonstration of estimation of *DeltaQT* and *DeltaRR* at arousal onset.

### 5.2.3 Measures of Cardiac Interval Variability

To estimate QT and RR fluctuation at arousal onset, we analysed $PRSA_{QT}$ and $PRSA_{RR}$ curves and computed $\Delta QT$ and $\Delta RR$ as the difference between average cardiac interval post and pre-onset (Figure **5.1**). Negative $\Delta QT$ or $\Delta RR$ indicate post-arousal interval shortening. The variance of QT as an indicator of QT variability was computed for each subject's $PRSA_{QT}$. To reach the normal distribution, we applied logarithm of variance ($logvarQT$). Similarly, $logvarRR$, the measure of RR interval variability was computed using $PRSA_{RR}$.

To investigate whether arousal duration can be effective in our analysis on CVD, arousals in each subject were classified into two groups short-term arousal with duration

$< 8$ and long-term arousal for longer episodes. Then, $QT_{STA}$, $QT_{LTA}$, $RR_{STA}$ and $RR_{LTA}$ were computed for each subject based using PRSA algorithm (**4.3.2.2**).

### 5.2.4 Statistical Analysis

Four extracted features of cardiac interval variability including $\Delta QT$, $\Delta RR$, *logvarQT* and *logvarRR* were divided into two parts with consideration of a threshold for Kaplan-Meier (KM) curve survival analysis and log-rank testing. The threshold was chosen when p-value of KM analysis reached the minimum value. For instance, $\Delta QT$ variable was divided into upper and lower $\Delta QT$ using threshold = 1.1 ($p = 0.0004$). Similarly for *logvarQT*, the threshold was chosen as 0.92 when $p = 0.067$. Participants information like their age, BMI or PASE score plus sleep scoring parameters (RDI and AI) were compared through student's two sample t-test. Their medical history and smoking habits were assessed using $\chi^2$ test. Cox proportional hazards regression models were constructed for continuous normalised variables and dichotomised and categorical variables.

## 5.3 Results

### 5.3.1 Participant characteristics

Table **5.1** presented detailed information about participants characteristics. At baseline visit, the participants' average age was $76.3 \pm 5.5$ and their BMI was $27.1 \pm 3.8$. Participants mean PASE score was as a measure of physical activity was $144.8 \pm 71.4$. About half of participants (49.3%) were overweight whilst more than one fifth of them were obese. Almost half of participants were hypertensive (n = 1321), whilst 16.5% of subjects were diagnosed with MI. Furthermore, 13.1% of men had diabetes, 5.1% had COPD, 9.1% had TIA. In addition 5.8% of participants had a past history of CHF whilst the prevalence of stroke was 3.5%. The participants respiratory disturbance index and arousal index were computed through as index of SDB events and sleep arousals in one hour of sleeping time. The average RDI and AI was $27.5 \pm 19.4$ and $25.1 \pm 12.4$, respectively.

### 5.3.2 Cardiovascular Mortality

The available outcome data of 2659 participant shows that during follow-up period ($10.7 \pm 4.1$ years), 1065 subjects (40.1%) were still alive, whilst 491 subjects (18.5%) died from CVD. In addition, various types of cancer was the reason of death of 305 participants (11.5%) and 581 of them (21.9%) died due to neither CVD nor cancer. There was no

| Variables | All<br>n = 2659 | $\Delta QT \leq 1.1$<br>n = 1769 | $\Delta QT > 1.1$<br>n = 890 | p-value | $\Delta RR \leq -8.8$<br>n = 1055 | $\Delta RR >$-8.8<br>n = 1604 | p-value | $logvarQT \leq 0.94$<br>n = 1724 | $logvarQT > 0.94$<br>n = 935 | p-value |
|---|---|---|---|---|---|---|---|---|---|---|
| Age | 76.3 ± 5.5 | 76.4± 5.4 | 76.3 ± 5.7 | *N.S* | 76.0± 5.4 | 76.6 ± 5.6 | **0.004** | 76.3 ± 5.4 | 76.4 ± 5.7 | *N.S* |
| BMI (kg/m2) | 27.2 ± 3.8 | 27.3 ± 3.9 | 27.0 ± 3.7 | **0.038** | 27.0 ± 3.5 | 27.3 ± 4.0 | **0.034** | 27.3 ± 3.8 | 26.9 ± 3.8 | **0.011** |
| Overweight | 1311 (49.3%) | 873 (49.3%) | 438 (49.2%) | *N.S* | 530 (50.2%) | 781 (48.7%) | *N.S* | 862 (50.0%) | 449 (48.0%) | *N.S* |
| Obese | 541 (20.3%) | 374 (21.1%) | 167 (18.8%) | *N.S* | 196 (18.6%) | 345 (21.5%) | 0.066 | 361 (20.9%) | 181 (19.3%) | *N.S* |
| PASE Score | 144.8 ± 71.4 | 141.8 ± 70.3 | 150.6 ± 73.3 | **0.003** | 150.0 ± 70.5 | 141.3 ± 71.8 | **0.002** | 145.0 ± 71.4 | 144.1 ± 71.5 | *N.S* |
| Medical History | | | | | | | | | | |
| HT | 1321 (49.6%) | 899(50.8%) | 422 (47.4%) | 0.097 | 517 (49.0%) | 804 (50.1%) | *N.S* | 881 (51.1%) | 440 (48.5%) | **0.045** |
| MI | 439 (16.5%) | 310 (17.5%) | 129 (14.5%) | **0.047** | 165 (15.6%) | 274 (17.1%) | *N.S* | 289 (16.7%) | 150 (16.0%) | *N.S* |
| TIA | 241 (9.1%) | 178 (10.1%) | 63 (7.1%) | **0.011** | 88 (8.3%) | 153 (9.5%) | *N.S* | 162 (9.4%) | 79 (8.4%) | *N.S* |
| CHF | 154 (5.8%) | 114 (6.4%) | 40 (4.5%) | **0.042** | 53 (5.0%) | 101 (6.3%) | *N.S* | 112 (6.5%) | 42 (4.5%) | **0.033** |
| Stroke | 94 (3.5%) | 74 (4.2%) | 20 (2.2%) | **0.011** | 28 (2.7%) | 66 (4.1%) | **0.046** | 58 (3.4%) | 36 (3.9%) | *N.S* |
| COPD | 136 (5.1%) | 101 (5.7%) | 35 (3.9%) | **0.049** | 40 (3.8%) | 96 (6.0%) | **0.012** | 85 (4.9%) | 51 (5.4%) | *N.S* |
| Diabetes | 347 (13.1%) | 240 (13.6%) | 107 (12.0%) | *N.S* | 135 (12.8%) | 212 (13.2%) | *N.S* | 232 (13.5%) | 115 (12.3%) | *N.S* |
| Smoking | | | | | | | | | | |
| Never | 1057 (39.8%) | 690(39.0%) | 367(41.2%) | *N.S* | 422(40.0%) | 635(39.6%) | *N.S* | 679 (39.4%) | 378(40.4%) | *N.S* |
| Past | 1550 (58.3%) | 1043(59.0%) | 507 (57.0%) | *N.S* | 615(58.3%) | 935 (58.3%) | *N.S* | 1015(58.8%) | 535 (58.2%) | *N.S* |
| Current | 52 (2%) | 36 (2.0%) | 16 (1.8%) | *N.S* | 18 (1.7%) | 34 (2.1%) | *N.S* | 30 (1.7%) | 22 (2.4%) | *N.S* |
| Sleep Index | | | | | | | | | | |
| RDI | 27.2 ± 19.4 | 27.9 ± 19.4 | 26.5 ± 19.3 | 0.071 | 25.5 ± 17.6 | 28.7 ± 20.4 | <**0.001** | 28.4 ± 19.6 | 25.7 ± 18.1 | <**0.001** |
| AI | 25.1 ± 12.4 | 25.8 ± 12.8 | 23.6 ± 11.4 | <**0.001** | 24.4 ± 12.2 | 25.5 ± 12.6 | **0.022** | 26.1 ± 12.5 | 23.2 ± 12.0 | <**0.001** |

**Table 5.1:** Study cohort detailed information. Subjects' anthropometric metrics, medical history, smoking habits and sleep indices were compared in lower and upper $\Delta QT$, $\Delta RR$ and *logvarQT* groups. BMI, HT, MI, TIA, CHF, COPD, RDI and AI refer to body mass index, hypertension, myocardium infarction, transient ischaemic attack, congestive heart failure, chronic obstructive pulmonary disease, respiratory disturbance index and arousal index, respectively. N.S also refer to non statistically significant results.

information about 217 subjects to clarify whether they were alive or died.

### 5.3.3 Univariate survival analysis

We applied Kaplan-Meier (KM) analysis to investigate whether the mortality rate is associated with cardiac interval variability during sleep arousals. $\Delta QT \leq 1.1$ ms referred to participants with post-arousal QT unchanged or shortening which included 67% of participants. KM curves of $\Delta QT$ does not show any significant relationship between the variable and CV mortality (Figure **5.2.a**). Participants with $DeltaQT \leq 1.1$ ms were more likely to be have higher BMI, less physical activity, history of MI, TIA, CHF, Stroke and COPD with higher number of arousals in their sleep (Table 1). However, $DeltaQT$ distribution was not associated with CV mortality in KM analysis ($p = 0.33$). Similarly, $logvarQT$ indicates the QT variability, where men with $logvarQT \leq 0.94$ had higher probability of history of hypertension and heart failure, higher degree of sleep apnoea ($RDI = 28.9 \pm 19.6$) and more fragmented sleep ($AI = 26.1 \pm 12.5$). The obtained p-value ($p = 0.067$) was close to the significant level, but greater and rejected the association of arousal-related QT variability and CV mortality (Figure **5.2.c**).

The negative $\Delta RR$ represents post-arousal RR shortening. Participants with $\Delta RR \leq -8.8$ ms were likely to be more physically active with less BMI and lower probability of stroke and COPD in their medical history with lower degree of RDI. KM curves of $\Delta RR$ demonstrate an elevated CV mortality in participants with $\Delta RR > -8.8$ ms in contrast with men with lower $\Delta RR$ (at 10.7 years, 20.1% vs 14.6%, $p = 0.0004$) (Figure **5.2.b**). Obtained results rejected the significant association between the distribution $logvarRR$ and CV mortality.

### 5.3.4 Cox-proportional hazard analysis

Table **5.2** shows the performance of Cox proportional hazard models. No significant association between arousal-related cardiac interval and CV mortality was observed. Even after adjusting Cox-proportional for age, BMI, PASE score, CHF, COPD, TIA, hypertension, stroke, RDI, AI and smoking, the performance of resulted model reject any statistical significance in association of QT or RR variability during arousals with CV mortality.

### 5.3.5 Arousal Duration and Cardiovascular Mortality

To assess the role of arousal duration in cardiac intervals fluctuation and its association with CV mortality, we computed $\Delta QT$ for $QT_{STA}$, $QT_{LTA}$ and $\Delta RR$ for $RR_{STA}$ and $RR_{LTA}$ in each

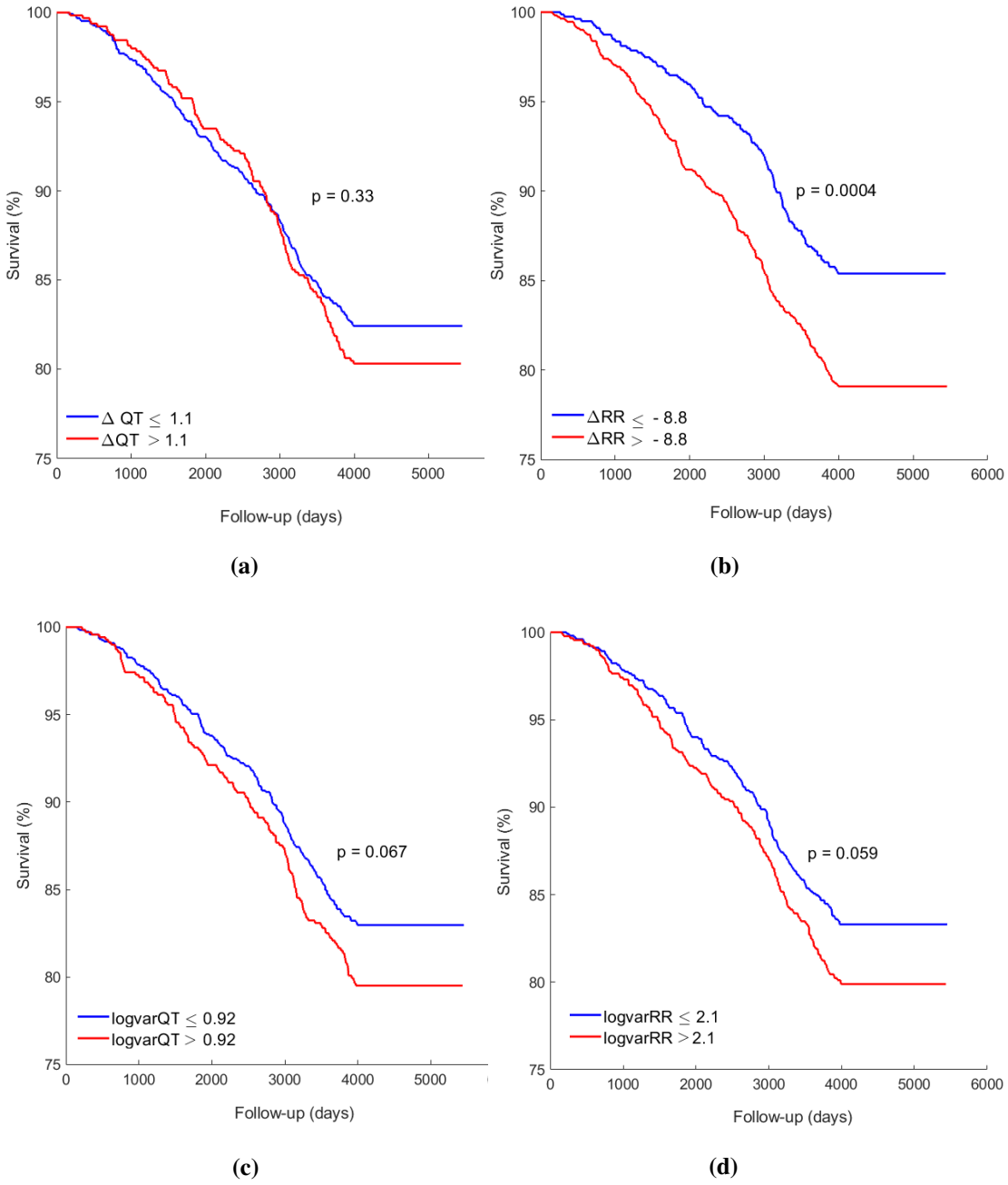



**Figure 5.2:** Kaplan-Meier survival analysis of participants based on QT and RR intervals **(a)** $\Delta QT$ at arousal onset **(b)**; $\Delta RR$ at arousal onset; **(c)** QT and **(d)** RR variances of arousal episodes in logarithmic scale; The obtained p-value indicate both analysis had an unsuccessful performance in prediction of CV mortality.

subject. The two sample t-test showed that the difference between $\Delta QT$ in short and long terms arousal was statistically significant ($p < 0.0001$). This means the QT variability at arousal onset is associated with duration of arousal. A similar t-test assessment confirmed that $\Delta RR$ in LTA and STA groups were significantly different ($p < 0.0001$) that indicates

| Variables | Uni-variate Analysis | | Multivariable Analysis | |
|---|---|---|---|---|
| | HR (95% Cl) | P-Value | HR (95% Cl) | P-Value |
| $\Delta QT$ | 1.2 (0.68 – 2.12) | 0.52 | 1.01 (0.99 – 1.02) | 0.59 |
| $\Delta QT$ >1.1 | 0.72 (0.34 – 1.54) | 0.39 | 0.98 (0.94 – 1.02) | 0.43 |
| $\Delta RR$ | 1.02 (0.64 – 1.64) | 0.9 | 0.99 (0.98 – 1.01) | 0.54 |
| $\Delta RR$ >-8.8 | 1 (0.99 – 1.01) | 0.26 | 1 (0.98 – 1.01) | 0.27 |
| $logvarQT$ | 1.09 (0.95 – 1.24) | 0.2 | 1.05 (0.98 – 1.01) | 0.52 |
| $logvarQT > 0.94$ | 1.14 (0.73 – 1.77) | 0.6 | 1.15 (0.75 – 1.17) | 0.32 |

**Table 5.2:** Cox proportional hazard regression assess the association of arousal related cardiac interval with cardiovascular mortality. HR and CI refer to hazard ratio and confidence interval.

RR fluctuations at onset also related to the duration of arousal.

Cox proportional hazard regression models based on $\Delta QT$ in both LTA or STA did not show any significant association with CV mortality either in univariate or multivariable analysis (Table **5.3**). Although the obtained p-value for $\Delta QT > 1.1$ in multivariable analysis was very close to significance level ($p = 0.08$). On the other hand, unadjusted Cox-proportional analysis indicates that $\Delta RR$ in long-term arousals has a significant association with CV mortality. Cox models based on both normalised $\Delta RR$ and $\Delta RR > -8.8$ ms variables in arousal longer than 8s had significant association with CV mortality ($p = 0.009$ and $p = 0.03$, respectively). In Cox multivariable analysis, normalised $\Delta RR$ in both LTA ans STA groups had significant association with cardiovascular mortality. This indicates RR fluctuations during the longer arousal had more effect than short arousal in CV mortality.

## 5.4 Discussion

The primary objective of the chapter was to find out whether cardiac interval fluctuations during arousals are associated with physical and medical history of subjects and if they are capable to predict CV mortality. This study was the first to investigate the prognostic value of sleep arousal cardiac interval variability for CV mortality. Obtained results show that $\Delta QT$ and $\Delta RR$ as two measures of cardiac interval changes at arousal onset are associated with several cardiovascular problems, respiratory disturbance index and participants

| Category | Variables | Uni-variate Analysis | | Multivariable Analysis | |
|---|---|---|---|---|---|
| | | HR (95% Cl) | P-Value | HR (95% Cl) | P-Value |
| STA | $\Delta QT$ | 1.004 (0.982 - 1.01) | 0.562 | 0.992 (0.978 - 1.006) | 0.251 |
| | $\Delta QT$ >1.1 | 0.997 (0.974 - 1.02) | 0.801 | 0.992 (0.969 - 1.016) | 0.513 |
| | $\Delta RR$ | 0.998 (0.996 – 1.001) | 0.143 | 0.997 (0.995 – 0.999) | **0.04** |
| | $\Delta RR$ >-8.8 | 1.004 (0.998 – 1.01) | 0.219 | 0.997 (0.996 – 1.009) | 0.385 |
| LTA | $\Delta QT$ | 1.004 (0.996 – 1.019) | 0.638 | 1.002 (0.998 - 1.017) | 0.761 |
| | $\Delta QT$ >1.1 | 0.982 (0.946 - 1.019) | 0.338 | 0.966 (0.929 - 1.004) | 0.08 |
| | $\Delta RR$ | 0.995 (0.992 – 0.999) | **0.009** | 0.995 (0.992 – 0.999) | **0.006** |
| | $\Delta RR$ >-8.8 | 1 (0.99 – 1.01) | **0.03** | 0.997 (0.991 – 1.003) | 0.223 |

**Table 5.3:** The effect of arousal duration in Cox-proportional hazard models of cardiac intervals and cardiovascular mortality. STA and LTA refer to short- and long-term arousal groups.

weight and physical activity. Although this association does not necessarily lead to increased CV mortality. The cohort study show a significant association between post arousal unchanged or descending QT ($\Delta QT > 1.1$ ms) and medical history of CVD such as MI, TIA, CHF, stroke and COPD. In previous chapter, we showed that sleep arousal occurrence are more likely to result QT shortening than QT prolongation. A considerable number of sleep arousals were induced by various adjacent SDB events like apnoea or hypopnoea. The greater number of SDB events result the numerous arousals and consequently more QT shortening episodes during the sleep. Furthermore, QT shortening is correlated with occurrence of arousals, where the correlation is stronger in RERA episode which induced by SDB events [74]. The increased probability of arousal-related QT shortening in men with CVD also indicates the association of sleep fragmentation and the likelihood of cardiovascular disease. Higher arousals either induced after SDB events or as EEG cortical modulation can intensify the degree of sleep fragmentation.

The cohort study shows the association of RR variability at arousal onset with subjects age, physucal activity and BMI . Patients with $\Delta RR > -8.8$ ms at arousal onset were more likely to had a medical history of COPD and stroke and higher respiratory disturbance index. A previous study showed that patients with both OSA and COPD have higher sympathetic

modulation of heart rate compared with those with OSA or COPD alone [185]. Our findings show subjects with history of COPD were likelier to have post-arousal RR prolongation and QT shortening and suffer from a severer degree of OSA.

According to the literature, sleep disordered breathing is highly associated with a range of CVD [92, 186, 187]. People suffering from OSA have a peak in sudden cardiac death during the sleeping hours, in compare with the nadir of SCD causes during this period in non-OSA people in the general population [92]. Kaplan-Meier survival estimator and Cox proportional models rejected the association of QT interval variability during arousal and CV mortality. The prognostic value of QT variability in prediction of CV mortality has been assessed in several studies [150, 188, 189]. Our study only focused on QT fluctuations during arousal activity that was not associated with CV mortality.

Different patterns of QT and RR variability in short- and long-term arousal groups, manifest the role of arousal duration in cardiac intervals variability. The distribution of $\Delta RR$ in LTA group had a significant association with CV mortality in spite of lack of similar association in STA group. The effect of arousal duration in RR variability has been illustrated in chapter 4 (Section **4.3.2.3**). Our observations in this chapter demonstrates again that arousal duration can be effective even in CV mortality prediction. The obtained hazard ratio ($HR = 0.998$) also shows RR interval Cox based model can not be considered as a robust predictor.

## 5.5 Conclusion

The general objective of this chapter was to study the association of sleep arousals and cardiovascular disease in a large cohort of old community-dwelling men. Measures of cardiac interval variability have been demonstrated to be associated with some cardiovascular diseases and subjects' physical characteristics. RR changes during long arousal episodes has been shown to be associated with cardiovascular mortality. Analysis of QT and RR variability during the sleep events is capable to be improved and applied for prospective studies about the association of different type of sleep apnoea/hypopnoea syndrome and cardiovascular disease. A similar cohort study in female subject could be very helpful to evaluate the role of gender in Cox cardiovascular analysis. Due to duration of an arousal episode (3-15 seconds), cardiovascular dynamics during arousal may not present enough information about nocturnal cardiac function to be able to predict CV mortality.

# Chapter 6

# General Conclusion

The general objective of this thesis was to present a comprehensive study on phenomenon of sleep arousal and its relations with dynamics of cardiovascular system. At this study, we firstly, developed a classifier model for automatic detection of sleep arousals. The suggested algorithm could distinguish 30 secs epochs with arousals from non-arousal epochs with high accuracy and sensitivity. In development of the algorithm, we accessed to only 9 subjects PSG datasets. For further studies, higher number of subjects, as well as the more machine learning techniques would help to reach a robust automatic algorithm for detection and classification of sleep arousal episodes.

At the second part of the thesis, five markers of cardiovascular activation including PTT, HF and LF spectral components of HRV as well as continuous systolic and diastolic BP (SBP and DBP) were computed and their modulations assessed before and after arousal onset. The study outcome manifests a post-arousal elevation in both blood pressure measures (SBP and DBP). In addition, we observed a PTT reduction at arousal onset regardless of arousal types.

The thesis also reported our effort to develop an algorithm for classification of sleep stages using only PTT and spectral features of HRV. The developed kernel model was evaluated in two group subjects (healthy and insomnia patients). Obtained results indicated that the algorithm could distinguish sleep stages regardless of the human subjects' conditions. Moreover, the suggested method requires fewer recordings and fewer electrodes. As a result it can be utilised for wearable technologies. An analysis with more subjects with a range of sleep disorders can improve the performance of suggested algorithm.

The manuscript also presented a new empirical polynomial model for overnight continuous BP estimation using the first derivation of PPG (VPG). It was the first to use VPG

signal for continuous BP estimation. The developed model could estimate SBP and DBP with low mean error and considerable $R^2$. It manifests the high correlation of VPG with both SBP and DBP variables.

Cardiac interval variability during arousals was also broadly investigated and discussed in fourth chapter of this manuscript. PRSA algorithm allowed us to analyse QT and RR variations before and after arousal onset. Gradients of cardiac intervals were developed to monitor instantaneous intervals changes. QT and RR gradients can provide detailed information about cardiac intervals pre- and post-onset fluctuations with consideration of arousal type, duration and the sleep stage that arousal episode occurs. In addition, the developed QT/RR linear correlation model reveals that their dependency is considerably increasing right after arousal induces. Our findings in this manuscript show an association between cardiac interval variability and arousal types. The respiratory or periodic limb movements related arousals caused more QT and RR variability in contract with spontaneous arousal episodes. Arousal indices are reversely related to both QT and RR variability where the higher number of arousals results a less variable interval.

The thesis also presents an investigation about the effect of sleep stage on cardiac intervals variability. Both arousal related QT and RR variability seem to be significantly associated with arousal sleep stages. However, more studies are required to determine about the effect of sleep stages in QT interval.

At final part of the thesis, our investigation about the arousal-related cardiac interval variability and subjects physical characteristics and medical history of cardiovascular disease has been reported. According to obtained results, the QT and RR changes at arousal onset are associated with several CV disease, BMI, physical activity, arousal index and RDI. The Kaplan-Meier analysis rejected any association of QT variability with cardiovascular mortality, whilst $\Delta RR > -8.8$ was significantly associated with CV mortality. The developed Cox proportional hazard regression model show that RR variability in longer arousal had prognostic value of CV mortality either in univariate analysis or in multivariable analysis with physical and medical background of participants, whilst shorter arousal did not. This manifests the effect of arousal duration in analysis. Although obtained hazard ratio indicates the capability of arousal-related RR and QT variability in prediction of CV mortality is limited.

Our research on MrOS study PSG datasets was limited on male subjects. A similar

study in females subjects, could assist to investigate the role of gender in cardiac interval analysis during the sleep arousal and its association with CV mortality. In this study, only the association arousal-related QT and RR variability with CVD was assessed. The cardiac interval variability during other physiological sleep phenomena like EEG cyclic alternating pattern (CAP), their association with various CVD and their prognostic values for CV mortality can be investigated in future studies. Furthermore, in this study, we found out that both QT and RR variability are associated with the possibility of COPD. A further study can reveal more details about QT and RR interactions either in sleep or wake in COPD patients.

Finally, we believe that the outcome of this study can be inspiring for biomedical engineers, cardio-respiratory physiologist, sleep scientists and whom are interested in signal processing and biomedical data analysis.

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