The Effect of Respiratory Event Type and Duration on Heart Rate Variability in Suspected Obstructive Sleep Apnea Patients

Master thesis

Salla Hietakoste

Faculty of Science

Biophysics

2020

Tiivistelmä

Uniapneapotilailla havaitaan usein matalaa pitkän aikavälin sykevälivaihtelua, jonka tiedetään myös olevan riskitekijä useille sydän- ja verisuonisairauksille. Ei kuitenkaan tiedetä, miten uniapneaan liittyvät erimittaiset hengityskatkot tai niiden tyyppi vaikuttavat yksittäisten hengityskatkojen aikaiseen ja jälkeiseen ultralyhyeen sykevälivaihteluun ja sydämen lyöntien väliseen kestoon, ts. RR-intervalleihin. Tässä tutkimuksessa tavoitteena oli tutkia ultralyhyen sykevälivaihtelun ja RR-intervallien sukupuolisidonnaisia muutoksia eri mittaisten apneoiden ja hypopneoiden aikana ja jälkeen. Hypoteesina oli, että pidemmät hengityskatkot aiheuttavat suurempia muutoksia hengityskatkojen aikaisen ja jälkeisen keskimääräisen RR-intervallien kestojen välille ja siten korkeampaa ultralyhyttä sykevälivaihtelua. Oletettiin myös, että apneat aiheuttavat suurempia muutoksia kuin hypopneat ja havaitut muutokset ovat suurempia miehillä kuin naisilla.

Potilasaineisto koostui 862 uniapneasta epäillyn potilaan sydänsähkökäyristä (EKG), jotka oli mitattu Prinsessa Alexandran sairaalassa (Brisbane, Australia) osana kliinistä unipolygrafiaa. Ultralyhyen sykevälivaihtelun määrittämiseen käytettiin keskimääräistä RR-intervallien kestoa ja aikatason sykevälivaihteluparametreja, jotka määritettiin hengityskatkojen aikaisista ja jälkeisistä (15 s hengityskatkon jälkeen) EKG-segmenteistä. Tutkittavat hengityskatkot jaettiin ryhmiin niiden tyypin (apneat ja hypopneat) ja keston (10 – 20 s, 20 – 30 s ja yli 30 s) perusteella. Lisäksi miesten ja naisten hengityskatkoja tutkittiin erikseen.

Tutkimuksessa havaittiin, että hengityskatkojen aikaisten ja jälkeisten RR-intervallien ero sekä ultralyhyt sykevälivaihtelu kasvoivat hengityskatkojen keston kasvaessa riippumatta sukupuolesta tai hengityskatkojen tyypistä. Havaittiin myös, että ero hengityskatkojen aikaisten ja jälkeisten sykevälivaihteluparametrien arvojen välillä pieneni hengityskatkojen pidentyessä riippumatta sukupuolesta tai hengityskatkojen tyypistä. Apneat kuitenkin aiheuttivat suuremman muutoksen kuin hypopneat, ja muutokset olivat suurempia miehillä.

Tulosten perusteella hengityskatkojen tyyppi ja kesto vaikuttavat ultralyhyeen sykevälivaihteluun ja RR-intervalleihin. Ultralyhyen sykevälivaihtelun ja hengityskatkojen ominaisuuksien huomioon-ottaminen uniapnean diagnostiikassa voisi olla hyödyllistä arvioitaessa taudin vakavuutta ja sydänterveyteen liittyviä riskejä. Tämän tutkimuksen tuloksista on kirjoitettu tieteellinen artikkeli Hietakoste ym. *Longer apneas and hypopneas are associated with greater ultra-short-term HRV in OSA*, joka on lähetetty vertaisarvioitavaksi alan kansainväliseen tieteelliseen julkaisusarjaan.

Abstract

Obstructive sleep apnea (OSA) patients have often reduced long-term heart rate variability (HRV) which is a known risk factor for several cardiovascular diseases such as hypertension and stroke. Albeit OSA being actively studied, it has remained uncharacterized how the duration and type of respiratory events affect the heart rate (HR), i.e. RR intervals, and ultra-short-term HRV during and immediately after the individual respiratory events. This study aimed to investigate whether the changes in ultra-short-term HRV and HR are modulated by the duration and type of the individual respiratory events and whether these changes are sex-specific. It was hypothesized that longer respiratory events cause higher ultra-short-term HRV and greater differences between RR intervals during and after the respiratory event. Moreover, it was hypothesized that the higher HRV and greater differences in HR are associated with apneas and men stronger than hypopneas and women.

Electrocardiograms (ECG) of 862 suspected OSA patients were collected during clinical polysomnography (PSG) at the Princess Alexandra Hospital (Brisbane, Australia) and they were analyzed retrospectively. Ultra-short-term HRV was studied with time-domain parameters determined from the ECG segments measured during (in-event) and 15 seconds after (post-event) the respiratory event. The respiratory events of all subjects were divided into groups based on the sex, the type of the respiratory events (apneas and hypopneas), and the duration of the respiratory events (10 – 20 s, 20 – 30 s, over 30 s).

A clear bradycardia-tachycardia rhythm associated with respiratory events was observed. The ultra-short-term HRV and the difference between in- and post-event RR intervals increased with increasing respiratory event duration. However, the difference between in- and post-event HRV parameter values decreased with increasing duration of the respiratory events. Furthermore, higher ultra-short-term HRV and a greater decrease in RR interval were observed in apneas and men.

Based on the results, the duration and type of the respiratory events modulate the HR and ultra-short-term HRV during and after the respiratory events, and these phenomena appear to be sex-specific. Therefore, considering the characteristics of respiratory events and ultra-short-term HRV could be useful in OSA diagnostics when estimating the OSA-related cardiac consequences. A scientific article based on the results of this thesis, Hietakoste *et al*. *Longer apneas and hypopneas are associated with greater ultra-short-term HRV in OSA*, has been submitted to a peer-reviewed scientific journal.

Table of contents

Abbreviations

AASM – American Academy of Sleep Medicine

AHI – Apnea-hypopnea index

ANS – Autonomic nervous system

APAP – Auto-titrating positive airway pressure

AV – Atrioventricular

BiPAP – Bi-level positive airway pressure

BMI – Body mass index

bpm – Beats per minute

CPAP – Continuous positive airway pressure

ECG - Electrocardiogram

EDS – Excessive daytime sleepiness

EEG – Electroencephalogram

EMG – Electromyogram

EOG – Electro-oculogram

HF – High-frequency

HR – Heart rate

HRV – Heart rate variability

ΔHRV_{Rel} – Relative change between in- and post-event HRV parameters (SD, RMSSD, or pRR50)

HSAT – Home sleep apnea test

LF – Low-frequency

N – Number of RR intervals

n_a – Number of apneas

n_d – Number of oxygen desaturations

n_h - Number of hypopneas

N1, N2, N3 – Sleep stages 1, 2, and 3 of NREM

NREM – Non-rapid eye movement

ODI – Oxygen desaturation index

OSA – Obstructive sleep apnea

p – Probability reflecting the statistical significance

PNS – Parasympathetic nervous system

PPG – Photoplethysmogram

pRR50 – Percentage of the number of successive RR intervals differing more than 50 ms

PSG – Polysomnography

REI – Respiratory event index

REM – Rapid eye movement

RMSSD – Root mean square of successive differences, i.e. RR intervals

RR interval – Period between two successive R peaks

RR_{AV} – Mean RR interval

ΔRR_{AV} – Difference between in-and post-event RR intervals

RR50, n_{RR50} – Number of successive RR intervals differing more than 50 ms

SA – Sinoatrial

SD – Standard deviation of RR intervals

SNS – Sympathetic nervous system

t_m – Total monitoring time

t_s – Total sleep time

TP – Total power

ULF – Ultra-low-frequency

VLF – Very-low-frequency

1. Introduction

Obstructive sleep apnea (OSA) is one of the most prevalent sleep disorders affecting globally almost 1 billion people according to the latest estimations [1]. OSA is diagnosed with the in-laboratory polysomnography (PSG), a gold-standard protocol that includes the recording of multiple biosignals, such as the electrocardiogram (ECG), respiratory signals (e.g. airflow via nasal pressure sensor), and the electroencephalogram (EEG, i.e. the electrical activity of the brain), or alternatively with ambulatory Home Sleep Apnea Test (HSAT) including a limited number of signals [2]. ECG is standardly recorded during the PSG, and it would be easily implemented in the HSAT. However, ECG or heart rate variability (HRV) parameters are not systematically utilized in current clinical practice related to diagnostics of OSA. The suitability of the ultra-short-term (< 5 min) ECG measurements has been studied for clinical HRV assessment [3, 4], although long-term (~ 24 h) and short-term (~5 min) analyses are considered to be the most suitable options for assessing HRV clinically [3, 5].

HRV is the interbeat variation of the heartbeats, i.e. variation of the RR intervals, caused by neuro-cardiac interactions and the autonomic nervous system (ANS) [3]. The ANS is divided into the sympathetic and the parasympathetic nervous systems (SNS and PNS). They operate together to maintain the homeostasis: normally, stress causes rapid SNS activation (e.g. fight-or-flight response) whereas the PNS is dominant at rest [6, 7]. Elevated SNS activity is related to shorter RR intervals and thus reduced long-term HRV in a healthy person, whereas longer RR intervals and higher long-term HRV reflect higher PNS activity [7]. During sleep, the sleep stages cause natural variation within the proportion of SNS and PNS activities [8].

In OSA, abnormal respiratory events, i.e. apneas and hypopneas, lead to intermittent hypoxemia, hypercapnia, pressure swings within the thorax, and recurrent arousals causing excess SNS activation and therefore reduced long-term HRV [9–11]. Moreover, elevated SNS activity can cause increased oxidative stress and vascular dysfunction [11] leading to possible structural and electrical cardiac remodeling [12]. Therefore, increased SNS activity elevates the risk of cardiovascular diseases, e.g. cardiac arrhythmias [11], stroke [13], and hypertension [14] in OSA patients.

Decreased long-term HRV has been observed in OSA patients, even during the daytime, [15, 16] and RR intervals have been shown to shorten with increasing OSA severity [17]. Previously, Sola-Soler *et al.* [18] showed in their study of eight patients that RR intervals shorten more after longer apneas.

However, larger and more comprehensive studies are required to study the connection between respiratory event duration and HRV. It has been shown that apnea-related oxygen desaturations are more severe when compared to those of hypopneas [19], and deeper desaturations are associated with a higher risk of cardiovascular diseases [20, 21]. Yet, it has remained uncharacterized how HRV is affected by the type of respiratory event. Furthermore, differences related to sex should be considered in HRV studies within OSA patients. While men have a higher risk for cardiovascular diseases, they have significantly higher long-term HRV and lower parasympathetic input to cardiac regulation compared to age-matched women [22]. In addition, OSA is more prevalent in men compared to women [23, 24] and men tend to have more severe OSA with longer respiratory events [10]. Moreover, study populations include markedly more or only men as subjects when investigating the connection between OSA and HRV [16].

This Master thesis aimed to study whether the respiratory event type and duration modulate the changes in RR interval within and after respiratory events and the ultra-short-term HRV and whether these modulations are sex-dependent. These aims were addressed by analyzing ECG recordings of 862 suspected OSA patients and comparing the time-domain HRV parameters between apneas and hypopneas, between respiratory events of different durations, and between men and women. This thesis hypothesized that ultra-short-term HRV increases as the duration of respiratory events increases due to pronounced RR interval prolonging during and shortening after apneas and hypopneas. It was also hypothesized that apneas would cause higher HRV and that these phenomena are stronger in men compared to women. Based on the results of this thesis, a scientific article, Hietakoste *et al*. *Longer apneas and hypopneas are associated with greater ultra-short-term HRV in OSA*, has been submitted to a peer-reviewed scientific journal.

2. Obstructive sleep apnea (OSA)

OSA is one of the most common sleep disorders. OSA patients suffer from complete or partial nocturnal breathing disruptions. A complete breathing cessation is called an apnea: the respiratory airflow decreases ≥ 90 % from the baseline for ≥ 10 s [2, 25]. If the respiratory airflow decreases ≥ 30 % for ≥ 10 s and there is arousal or ≥ a 3 % drop in oxygen desaturation related to the respiratory event, the event is called a hypopnea [2, 25]. Earlier, the respiratory event was defined as a hypopnea if there was ≥ a 4 % drop in oxygen desaturation [26]. Respiratory events lead to intermittent oxygen desaturations, arousals from sleep, and other physiological consequences [10, 27]. Intermittent desaturations activate the sympathetic nervous system (SNS) repeatedly [9, 28] and arousals cause sleep fragmentation [28, 29]. Due to these factors, OSA patients have excessive daytime sleepiness (EDS) and impaired vigilance increasing the risk for traffic accidents and importantly, have elevated risk for cardiovascular diseases [28–30].

The diagnostic criteria of OSA rely on guidelines of the American Academy of Sleep Medicine (AASM) [2]. The current clinical parameter used to assess the severity of OSA and the necessity of treatment is the apnea-hypopnea index (AHI), which is solely based on the number of apnea and hypopnea events per hour of sleep [2]. Based on the AHI, patients are classified into four different OSA severity groups: no-OSA (AHI < 5), mild OSA (5 ≤ AHI < 15), moderate OSA (15 ≤ AHI < 30) and severe OSA (AHI ≥ 30) [2, 25]. Albeit AHI is the most commonly used parameter in OSA diagnostics, it is insufficient parameter alone in OSA severity assessment since it does not consider the duration of respiratory events, the severity of the associated blood oxygen desaturation events, or physiological changes that respiratory events may cause [31, 32].

2.1. Epidemiology and economic burden of OSA

The estimated prevalence of OSA varies greatly depending on the used diagnostic methods and the criteria for hypopneas [25, 33]. In Finland, at least 300 000 adults suffer from OSA [34], but it has been estimated that the number of OSA patients (AHI ≥ 5) may be up to 1.5 million [1]. Senaratna *et al.* [35] reported that the global prevalence of OSA (AHI ≥ 5) in the adult population is 9 – 38 % and 6 – 17 % adult population suffer from moderate or severe OSA (AHI ≥ 15). The prevalence of OSA increases with age and obesity [23, 35, 36], and the most recent estimation is that globally almost 1 billion people are affected by OSA [1]. OSA is more common in men compared to women

[10, 23], but the probability of getting OSA increases in women after menopause [37]. For example, Heinzer *et al.* [24] have shown that 49.7 % of men have severe or moderate OSA whereas the prevalence in women was only 23.4 %. The prevalence of OSA has increased over time most likely due to increased obesity [38, 39], and approximately 70 % of the population diagnosed with OSA are obese [40]. Despite the awareness of OSA has increased in the last decades it is an underdiagnosed disease: it has been estimated that over 80 % of the population with OSA are still undiagnosed [41].

The consequences of undiagnosed OSA, losses in both economic and well-being, are extensive. As OSA remains untreated, the risk for comorbidities and daytime sleepiness increases in OSA patients leading to an elevated risk for motor vehicle and workplace accidents and losses in productivity [30, 42]. Frost & Sullivan [30] has estimated that the costs of diagnosis and treatment of OSA are approximately $ 2 100 per patient whereas the cost burden of undiagnosed OSA can be up to $ 6 400 per patient due to comorbidities, accidents and lost productivity. Hillman *et al.* [42] have estimated that the total burden of financial and nonfinancial costs of patients with inadequate sleep was approximately $ 25.41 billion in Australia between 2016 – 2017. Inadequate sleep of these patients was due to sleep disorders such as OSA. Within the same patients, the number of lost years of healthy life due to a disability or premature death was approximately 173 000 in 2016 – 2017. Albeit these estimates are large, they may still underestimate the economic burden of OSA and inadequate sleep [42].

2.2. Pathophysiology and risk factors

The pathophysiology of OSA is highly individual and several factors contribute to it, including for example abnormal anatomy of the pharynx, increased adipose tissue around upper airways, impaired physiology of muscles and nerves of upper airways, and decreased arousability [27, 29]. Especially the impaired function of genioglossus muscle predisposes to obstructions of the upper airways [43, 44]. Upper airways remain open during wakefulness due to higher activity of airway dilatator muscles, but during the sleep, the airways are more prone to collapsing due to decreased muscle activity [27].

The pharynx is a complex anatomic structure of muscles and other soft tissues: it participates in speech production, swallowing and it protects the lower airways from pathogens [29, 45]. It does

not have a rigid or bony supporting structure: upper airways are momentarily able to close and change shape voluntarily for example during speech and swallowing, but this also allows the airways to collapse involuntarily during sleep [29]. The pharynx is divided into three parts: nasopharynx, oropharynx, and laryngopharynx, of which oropharynx is the most prone to obstructions [43, 45]. Moreover, OSA patients tend to have a smaller cross-sectional area of the upper airways [45, 46], and narrower airways collapse more easily than wider [29].

The cortical arousal from sleep is a reflex mechanism to protect the body from hypercapnia (i.e. excess carbon dioxide in the blood) due to upper airway obstruction [47]. The muscles of the pharynx activate quickly due to arousal to open the airways and recover the breathing to its normal level leading to normalization of respiratory gas levels in blood [28, 29]. Low arousal threshold is beneficial for the recovery of oxygen desaturation and muscle activity, but it may amplify the cyclical breathing pattern during sleep thus fragmenting sleep and leading to EDS [29, 47].

Obesity is one of the biggest risk factors for OSA [28, 35, 48], yet it is also a significant factor in OSA pathophysiology [41]. Excess adipose tissue deposits around the upper airways decrease the cross-sectional area of the airways making it more prone to collapse and it has been shown to impair the function of airway dilatator muscles [49]. Moreover, increased adipose tissue deposit in the abdominal area decreases the lung volume leading to deeper oxygen desaturations during apneas and hypopneas [28, 29]. Therefore, weight loss has been shown to decrease the severity of OSA and the number of respiratory events in OSA patients [49, 50]. In addition, obesity is a risk factor for cardiovascular diseases and type 2 diabetes mellitus, which both are significant risk factors for OSA [40].

Other risk factors for OSA are male sex, older age, and smoking. OSA is shown to be more prevalent in men compared to women, most likely due to differences in anatomy, the activity of soft tissues and muscles of upper airways, and in hormonal regulation of breathing [51, 52]. However, the prevalence of OSA in women increases after menopause [37, 53] supporting the theory of hormonal effects on differences in OSA prevalence between men and women. The impairment in upper airway muscles and the changes in soft tissues due to decreased collagen production are thought to be the reason why higher age is a risk factor for OSA: elasticity of the soft tissues decreases with age leading to the higher probability of upper airway collapses [27, 54]. It has also been noticed that the adipose tissue increases around the upper airway with aging despite the systemic fat [29]. Smoking has also

a significant effect on the pathophysiology of OSA. Smokers have markedly increased risk for OSA, most likely due to inflammatory states of upper airways caused by smoking and due to restless sleep [55, 56].

The prevalence and severity of respiratory events are also dependent on the sleep stage and sleeping position. Sleep stages are divided into two categories: NREM (non-rapid eye movement) and REM (rapid eye movement). NREM is further divided into two stages of light sleep (N1 and N2) and into one stage of deep sleep (N3) [2]. In NREM, the physiological processes and the electrical functioning of the brains slow down towards deeper sleep stages [57]. In REM, the activity of SNS increases leading to increased blood pressure, HR, and electrical activity of the brain [57]. Respiratory events are more frequent, and they are usually longer in REM sleep compared to NREM leading to deeper oxygen desaturations during respiratory events [29, 51, 58]. The proportion of REM sleep, and thus the number and duration of respiratory events increases towards the morning [59, 60]. Similarly, respiratory events in the supine sleeping position are more frequent and longer compared to events in the non-supine sleeping position [61].

2.3. Symptoms

OSA is characterized by several symptoms that can be divided into daytime and nocturnal symptoms (Table 2.1). The most common daytime symptom of OSA is excessive daytime sleepiness (EDS) [51, 62, 63]: approximately 15 – 42 % of OSA patients suffer from it [64]. EDS is caused by sleep fragmentation and hypoxemia. The sleep fragmentation prevents the brain from falling into an undisturbed deep sleep due to intermittent SNS activations caused by arousals [28, 29]. Furthermore, the nocturnal respiratory events cause oxygen desaturations and further hypoxemia leading to activation of the SNS even without arousals [65]. Together, sleep fragmentation and hypoxemia increase the physiological stress of the body. EDS can be experienced as fatigue or exhaustion, not necessarily as sleepiness, which makes it harder to recognize and interpret the EDS [66, 67]. Moreover, EDS can impair cognitive performance with other factors [51, 68] leading potentially to several mood disorders and memory problems [68, 69]. Headache after awakening is also a typical symptom of OSA: at least 18 – 29 % of patients suffer from it [70] although some studies have estimated the prevalence to be over 45 % [71]. For example, the nocturnal variation of

blood oxygen saturation and excess carbon dioxide due to respiratory events are thought to be the reason for OSA related headaches [71–73].

Table 2.1. Common daytime and nocturnal symptoms of OSA [51].

Daytime	Prevalence (%)	Nocturnal	Prevalence (%)
Excessive sleepiness	15 – 42 [64]	Snoring	70 – 95 [64]
Involuntary periods of sleep	23 – 29 [64]	Sweating	50 [64]
Headache	18 – 29 [70]	Nocturia	28 [64]
Memory problems	66 [67, 68]	Heartburn	54 – 76 [74]
Concentration problems	78 [67, 68]	Dry mouth	74 [64]
Mood disorders	7 – 70 [69, 70]	Insomnia	28 – 59 [75]
Impotence	30 [64]	Awakening accompanied by choking	18 – 31 [64]

OSA = Obstructive sleep apnea

The most prevalent nocturnal symptom of OSA is snoring [51, 62, 76]. Most of the snorers suffer from OSA, yet snoring is not always a symptom of OSA and every OSA patient does not snore [51, 77, 78]. Over 70 % of OSA patients are snorers [64] and the prevalence of the snoring as an OSA symptom has been estimated to be even up to 95 % [64]. Snoring is caused by a partial obstruction of upper airways in the area of the oropharynx and it occurs mostly in the supine sleeping position [56]. Another common nocturnal symptom is sweating: approximately half of OSA patients suffer from it [64] and the prevalence of night sweats is 3-fold in OSA patients compared to the healthy population [79]. Night sweats are most likely caused by elevated SNS activity [80] due to intermittent hypoxemia. In addition to snoring and night sweats, dry mouth and insomnia are common symptoms in OSA patients. Dry mouth is associated with decreased salivation, but the more probable reason for dry mouth is sleeping mouth open [64, 81]. Patients with severe OSA are shown to report mouth dryness more often compared to patients with mild OSA [81]. As for insomnia, arousal from sleep and SNS activation may increase alertness and prevent OSA patients to fall asleep again [75]. It has been proposed that insomnia increases the severity of OSA and those patients experience often symptoms of mood disorders such as anxiety and depression [82].

2.4. Comorbidities

OSA patients are often multimorbid [27, 83]: some of the comorbidities are caused by OSA risk factors, e.g. obesity, whereas some may be caused directly by respiratory events and their consequences [27, 51]. Long follow-up studies have shown that risk for sudden death is significantly increased in OSA patients [84, 85]. Young *et al.* [85] have shown that even after the removal of factors elevating the risk of sudden death, such as age and obesity, the mortality was nearly 4-fold during an 18-year follow-up period in patients with untreated severe OSA compared to patients without OSA. Therefore, untreated OSA is strongly associated with an increased probability of sudden deaths [85]. Punjabi *et al.* have shown similar results: in OSA, the risk for all-cause mortality is elevated especially in men aged 40 – 70 years [86].

Several comorbidities of OSA are among cardiovascular diseases (Table 2.2). The respiratory events, apneas, and hypopneas lead to oxygen desaturations and further intermittent activations of SNS [9–11]: this burdens the circulatory and neurohormonal regulatory systems [87]. When the patient tries to breathe despite the obstructed airways the negative intrathoracic pressure increases leading possibly to vasoconstriction of thoracic blood vessels [11, 65]. Therefore, OSA patients have an elevated risk of heart failure [65, 88]. Arousals and further increased SNS activity affect the regulation of the circulatory system and blood pressure [65]. Nocturnal blood pressure and HR cannot return to their normal levels due to increased SNS activity, and this is thought to be the most likely reason for increased numbers of hypertensive OSA patients compared to healthy controls [24, 89]. It has been shown that OSA patients have over 6-fold risk to develop hypertension, and even after considering the effect of obesity, age, and smoking, the risk is over 2-fold [24, 90]. OSA patients have also markedly increased risk for arrhythmias due to increased hypoxemia-induced pulmonary hypertension, negative intrathoracic pressure, and sympathetic tone [11, 91]: the risk for arrhythmias is increased nearly an 18-fold shortly after individual respiratory events [92].

Table 2.2. Prevalent comorbidities of OSA patients and their relative risks compared to non-OSA patients.

Comorbidity	Relative risk
Hypertension	1.6 – 6.8 [24, 89, 90]
Coronary artery disease	4.6 [93]
Atrial fibrillation	2.2 – 4.0 [94, 95]
Stroke	2.0 – 4.0 [13, 96]
Heart failure	2.0 – 2.4 [88, 97]
Diabetes mellitus, type 2	2.0 [24]

OSA = Obstructive sleep apnea

2.5. Diagnostics

The diagnostics of OSA is currently based on clinical sleep studies and the interviews of the suspected patient and possible living companion. Interviews survey the clinical picture of symptoms (e.g. EDS, snoring) and risk factors (e.g. obesity, smoking), and based on the interview, the patient is referred to a clinical sleep study [51]. A gold standard for clinical diagnostics of OSA is the in-laboratory polysomnography (PSG) being more thorough, but in some countries, such as in Finland, the home sleep apnea test (HSAT) is more often used due to its better accessibility and cost-effectiveness [51, 98].

PSG is conducted at the hospital or in a sleep laboratory. It records the electrical activity of the brain and heart, oxygen saturation of the blood, movement of the eyes and legs, breathing, sleeping position, and snoring [2, 83, 99]. Electroencephalography (EEG) is used to assess the electrical activity of the brain and identify the sleep stages [2]. The electrical function of the heart is measured with the electrocardiogram (ECG) and pulse oximetry is used for determining the blood oxygen saturation. The movement of the eyes and facial (chin) muscles are measured with electro-oculography (EOG) and electromyography (EMG), respectively. Breathing during apneas is assessed with measuring the respiratory airflow with the thermistor and during hypopneas with the nasal pressure sensor [2]. Moreover, breathing is assessed by measuring the movement due to breathing with respiratory belts around the thorax and diaphragm [2]. The type of apnea can be determined with analysis of breathing movements: the respiratory movement continues through obstructive apnea but in central apnea, they stop [2]. Mixed apneas contain characteristics of both types starting usually as central and turning into obstructive apneas [2]. Sleeping position is determined with

accelerometer and snoring is registered either by audio recording or by registering the vibrations due to snoring with a piezoelectric sensor. Moreover, video recording is used to assess visually the restless sleep and awakenings.

In addition to PSG, HSAT is a clinically approved method for OSA diagnostics. It is conducted usually at the home of the suspected patient making HSAT more cost-effective and comfortable compared to PSG conducted at the hospital [98–100]. HSAT differs from PSG by the number of recorded signals: neither EEG, EOG, nor EMG are recorded during HSAT [2]. Therefore, it is not possible to determine the total sleep time or the sleep stages based on HSAT, and e.g. total sleep time must be estimated from the other signals. Due to lack of EEG recording, arousals, or hypopneas related to them cannot be recognized in HSAT [98]: the severity of OSA may be underestimated using HSAT [33, 98]. Despite the potential differences in OSA severity between diagnostic methods, HSAT is precise enough as a method for OSA diagnostics and it can be safely used instead of PSG [98]. However, HSAT is not suitable for all OSA patients, and therefore, PSG is recommended as a primary diagnostic method for OSA patients with e.g. severe insomnia, movement disorders related to sleep, or severe cardiorespiratory disease [100].

Using PSG, the OSA diagnosis is made based on the apnea-hypopnea index (AHI), the number of respiratory events per hour of sleep (2.1). The oxygen desaturation index (ODI), the number of desaturations per hour of sleep (2.2), may be used in addition to AHI [2]. When HSAT is used, the diagnosis is based on respiratory event index (REI), the number of respiratory events per hour of recording (2.3), due to lack of the EEG.

$$AHI = \frac{n_a + n_h}{t_s}, [h^{-1}] \tag{2.1}$$

$$ODI = \frac{n_d}{t_s}, [h^{-1}] \tag{2.2}$$

$$REI = \frac{n_a + n_h}{t_m}, [h^{-1}] \tag{2.3}$$

in which n_a, n_h, and n_d are the total numbers of apneas, hypopneas, and oxygen desaturations, respectively. t_s and t_m are the total sleep time and total monitoring time, respectively, both usually expressed as hours. The AHI is the most used from these parameters and it is used for the assessment of the OSA severity [25, 99]. It has been recommended that the severity of EDS should be included in the assessment of OSA severity in addition to AHI, and the final severity categorization

should be chosen by the more severe parameter (Table 2.3) [25]. The problem with AHI, ODI, and REI is that they do not consider the severity of individual respiratory events or their physiological consequences. For example, an apnea lasting 10 seconds is considered to affect AHI, ODI, and REI similarly as a 60-second apnea. The duration of respiratory events has been shown to vary within patients with similar AHI [101], and longer respiratory events lead to deeper oxygen desaturations [19]. Moreover, patients with severe OSA have been shown to have longer respiratory events compared to patients with mild or moderate OSA, but paradoxically, the AHI cannot increase along with the increasing respiratory event duration [101].

Table 2.3. Assessment of OSA severity based on AHI and EDS [25].

Severity	AHI	EDS
Mild	5 ≤ AHI < 15	Unwanted sleepiness and/or involuntary sleep episodes occurring during activities requiring little attention. Symptoms produce minor occupational or social function impairment.
Moderate	15 ≤ AHI < 30	Unwanted sleepiness and/or involuntary sleep episodes occurring during activities requiring some attention. Symptoms produce moderate occupational or social function impairment.
Severe	AHI ≥ 30	Unwanted sleepiness and/or involuntary sleep episodes occurring during activities requiring active attention. Symptoms produce major occupational or social function impairment.

OSA = Obstructive sleep apnea, AHI = Apnea-hypopnea index, EDS = Excessive daytime sleepiness

2.6. Treatment

The most common treatment method is continuous positive airway pressure (CPAP) treatment [27, 83]. CPAP machine includes an external air pump, hose, and nasal mask. With the CPAP machine, a continuous airflow is produced into the airway of the patient preventing the obstructions of the upper airways [102, 103]. CPAP treatment helps to reduce the symptoms of OSA even after first nights of treatment: it effectively decreases the number of respiratory events decreasing for example the snoring and EDS [62, 103]. CPAP treatment does not necessarily reduce the risk for cardiovascular diseases but it decreases hypertension in OSA patients [104, 105]. CPAP treatment is mainly used for patients with moderate and severe OSA (AHI > 15) [51], but this is an arbitrary decision of the healthcare professionals; CPAP treatment has shown to increase the quality of life

of patients with mild OSA in addition to patients with moderate or severe OSA [106]. CPAP treatment adherence is relatively low: only 60 – 70 % of patients commit to CPAP therapy [27]. Low adherence level to treatment may be due to discomfort of the mask [62, 103] and some patients also suffer from dryness of nose and mouth and allergic reactions. Alternative treatments for patients to who CPAP is not suitable are bilevel positive airway pressure (BiPAP) and auto-titrating positive airway pressure (APAP) [27, 107]. The difference of BiPAP to CPAP therapy is adjusted positive pressure instead of continuous pressure: the machine adjusts the pressure according to inspiration and expiration. BiPAP may be preferred if the patient has expiratory pressure discomfort [27]. In APAP, the positive pressure is varied based on, for example, sleep stage or sleeping position [27].

Weight loss and long-term changes in living habits are essential in the treatment of OSA, especially for obese patients [51, 62]. Weight loss has been shown to decrease the number of respiratory events, especially short apneas and hypopneas, and thus reduce the severity of OSA [102, 108]: even 3 – 18 % weight loss can reduce the AHI over 60 % [109]. Moreover, weight loss can decrease the effects of OSA risk factors and may even prevent the occurrence of comorbidities [103, 109].

Positional sleep apnea can be treated with conservative positional treatment that prevents the OSA patient from sleeping in a supine position in which respiratory events are more frequent [61, 62]. Options for positional therapy are, for example, a tennis ball attached to the back of the nightwear, a pillow under the back, or a sleep apnea belt. Mild OSA can be treated with oral devices that move the jaw of the patient forward making the upper airways wider and thus preventing the obstructions and snoring [27]. Moreover, a variety of surgical operations can be used to widen the upper airways and thus preventing respiratory events [110]. These operations may be chosen over other therapies for example due to abnormal anatomy of upper airways.

3. Heart rate variability (HRV)

Seemingly steady resting heart rate of a healthy subject is naturally highly irregular due to continuous regulation by neuro-cardiac interactions. This beat-to-beat variation is called heart rate variability (HRV). It is a useful, non-invasive tool for assessment of the autonomic regulation of cardiac functions [111]. HRV is regulated via the autonomic nervous system (ANS). HRV can be divided into three categories based on the time interval used to determine the HRV. The period used to measure long-term HRV varies from hours to days, but usually, it is measured with 24 h Holter-ECG [3]. Short-term HRV measurements last for approximately 5 minutes whereas HRV measurements lasting << 5 minutes are called ultra-short-term HRV [3]. Long-term and short-term recordings are the recommended HRV measurements. Yet, the ultra-short-term measurements have shown promise in HRV analysis [3, 4]. HRVs of different time-interval, for example, long-term and short-term HRV, are not interchangeable, and thus they cannot reliably be compared to each other [3].

3.1. Autonomic nervous system

ANS is the most important system regulating HRV. It cannot be affected directly with voluntary actions, but these actions can affect the activity of ANS indirectly. ANS is regulated by the medulla of the brainstem, limbic system, and hypothalamus, from which medulla regulates breathing and the functioning of the heart and vascular system [80]. ANS is divided into sympathetic and parasympathetic nervous systems (SNS and PNS, respectively) and enteric division. The enteric division can function independently, but it is mainly controlled by SNS and PNS [80]. Typically, the homeostasis of viscera is controlled by both SNS and PNS while they usually regulate the viscera in a contradictory manner [7, 80, 111]. For example, SNS increases the heart rate (HR) whereas PNS decreases it. The functioning of the target organ is determined by the balance of the SNS and PNS activities.

SNS is mainly activated through physical activity and stress [80]. Sympathetic activation can lead either to massive, non-specific or discrete, organ-specific responses. Strong SNS activation prepares the body for stressful situations via survival mechanism, the flight-or-fight response, by activating several body functions simultaneously. For example, increased SNS activity leads to increased blood

pressure, and sweating, increased blood glucose levels and decreased insulin secretion, increased blood circulation in skeletal muscles, and decreased gastrointestinal activity (Table 3.1) [80]. Moreover, increased SNS activity increases HR due to the increased release of noradrenaline in sympathetic synapses [80, 111]. This also increases the conduction velocity of neural impulses in the conduction system of the heart and thus increases the contractility of the heart [80, 111]. Increased HR leads to decreased long-term HRV, that is associated with several morbidities and all-cause mortality, such as OSA, hypertension, coronary artery disease, diabetes mellitus, heart failure, and myocardial infarction [7, 15, 112] most likely due to increased relative SNS activity and reduced regulatory capacity [7, 111]. SNS regulates HR effectively in frequencies below 0.10 Hz [5] and exerts its effects relatively slowly, in 5 – 30 seconds, due to slow reabsorption and metabolization of noradrenaline [111, 113]. All sympathetic neurons emerge from the thoracic and upper lumbar spinal cord (T1 – L3) [80].

Table 3.1. The physiological effects of sympathetic and parasympathetic nervous systems (SNS and PNS, respectively) on the viscera [80, 114].

Target organ	SNS	PNS
Heart	Heart rate increases Contraction force increases	Heart rate decreases
Lungs	Dilates bronchi	Constricts bronchi
Eyes	Dilates pupils	Constricts pupils
Sweat glands	Increases sweating	
Stomach	Inhibits digestion	Stimulates digestion
Liver	Stimulates the production and release of glucose	
Intestines	Inhibits peristalsis	Stimulates peristalsis
Urinary bladder	Relaxes the bladder	Contracts the bladder

While SNS activates due to stress, PNS is dominant at rest leading to a resting HR of approximately 75 beats per minute (bpm) [7, 80]. Opposing SNS, PNS acts only organ-specifically mediating reflexes to the target organs [80]. For example, PNS increases the gastrointestinal activity, stimulates digestion, constricts airways, and slows the HR (Table 3.1) [80]. The slowing of HR is mediated through the excretion of acetylcholine in parasympathetic synapses [80, 111]. Acetylcholine

decreases the conduction velocity of neural impulses in the conduction system of the heart leading to decreased HR and increased HRV [80] and further reflecting normal regulatory capacity [7, 111]. Acetylcholine has a very short latency period and thus the effects of PNS are almost immediate (< 1 s) [111, 113]. This enables PNS to regulate HR on a beat-to-beat basis in a frequency range of 0 – 0.5 Hz [5]. Parasympathetic neurons controlling vital functions, such as breathing and the functioning of the heart, emerge from the medulla via the tenth cranial nerve (CN X, *nervus vagus*) [80].

3.2. Heart and HRV

The human heart is a muscular pump consisting of two atria and two ventricles and weighing 250 – 350 grams (Figure 3.1, based on [114]) [7]. Oxygenated blood flows through the left atrium to the left ventricle and is pumped from there the aorta and further systemic circulation [80, 114]. On the left side of the heart, the atrioventricular valve (mitral valve) prevents the blood flowing from the ventricle to the atrium, and aortic valve prevents the blood from returning to the ventricle [114]. Deoxygenated blood flows through the right atrium and is pumped from the right ventricle to the pulmonary circulation [80, 114]. The tricuspid valve prevents deoxygenated blood from flowing back to the right atrium from the right ventricle and the pulmonary valve stops the blood returning to the right ventricle [114].

The main components of the conductive system of the heart are the sinoatrial (SA) and atrioventricular (AV) nodes, the bundle of His, and the Purkinje fibers (Figure 3.2, based on [80]) [80, 114]. The pacemaker of the heart, SA node in the right atrium, generates action potentials spontaneously causing also the AV node to fire action potentials [7, 80, 114]. This leads to depolarization and thus contraction of the atria. The action potentials of the AV node are conducted through the bundle of His to the upper septum of the heart [80, 114]. From there the action potentials are conducted to the ventricular myocardium via Purkinje fibers leading to the depolarization and further contraction of the ventricles [7, 80]. Without the cardiac regulation by the ANS and hormonal activity, the intrinsic HR initiated by the SA node can be over 100 bpm, but the average HR is approximately 75 bpm mostly due to PNS activity [80, 115].

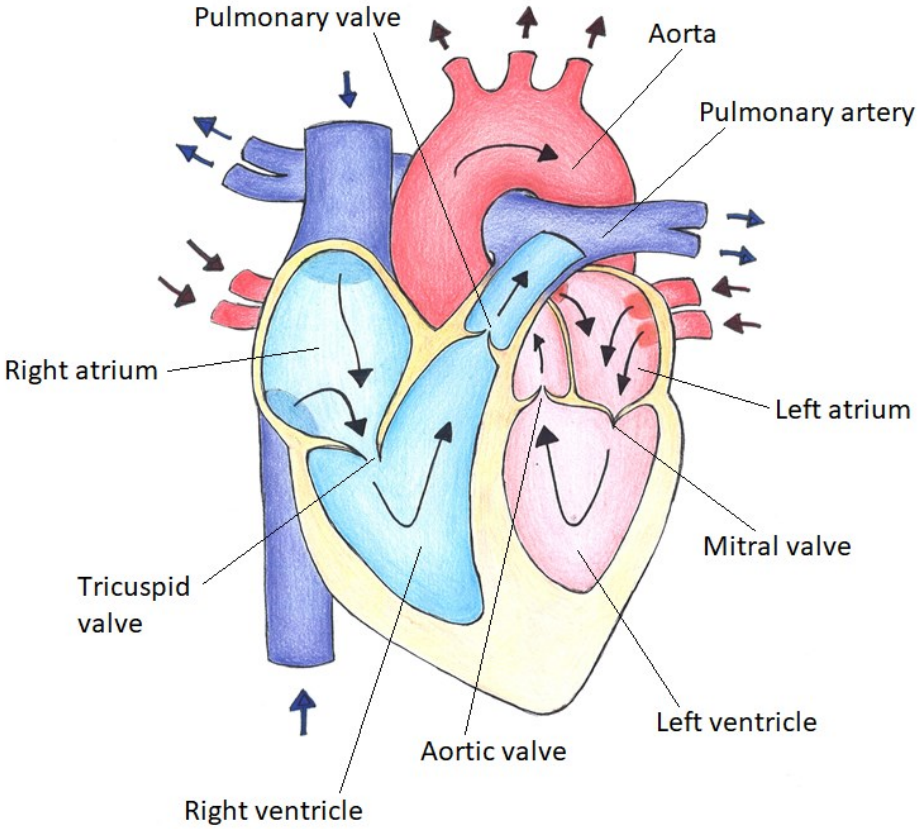

Figure 3.1. The physiology of the heart. The blood is pumped from the atria to ventricles from where it is pumped to the aorta and pulmonary arteries. Arrows indicate the direction of the blood flow.

The electrical activity of the heart, and thus HR, is measured with ECG. Standard ECG is measured with 12 leads, but for example in OSA diagnostics lead II is used as a standard ECG [2]. The movement of action potentials through the cardiac myocytes generate small extracellular electrical signals, and thus the electrical field produced by the cardiac function can be measured as a potential difference with electrodes attached to the skin. Normal ECG can be divided into P, Q, R, S, and T waves [80, 114]. The depolarization of the atrial myocardium produces the P wave, whereas the QRS complex and T wave represent the de- and repolarization of the ventricular myocardium, respectively (Figure 3.3, based on [80]) [80]. According to the established practice, the high R wave, or R peak, is used to determine the HR. HRV is defined as the variation of successive heartbeats, i.e. interbeat intervals [111]. HRV can be also obtained from the pulses of the photoplethysmography (PPG) signal recorded with a pulse oximeter [7].

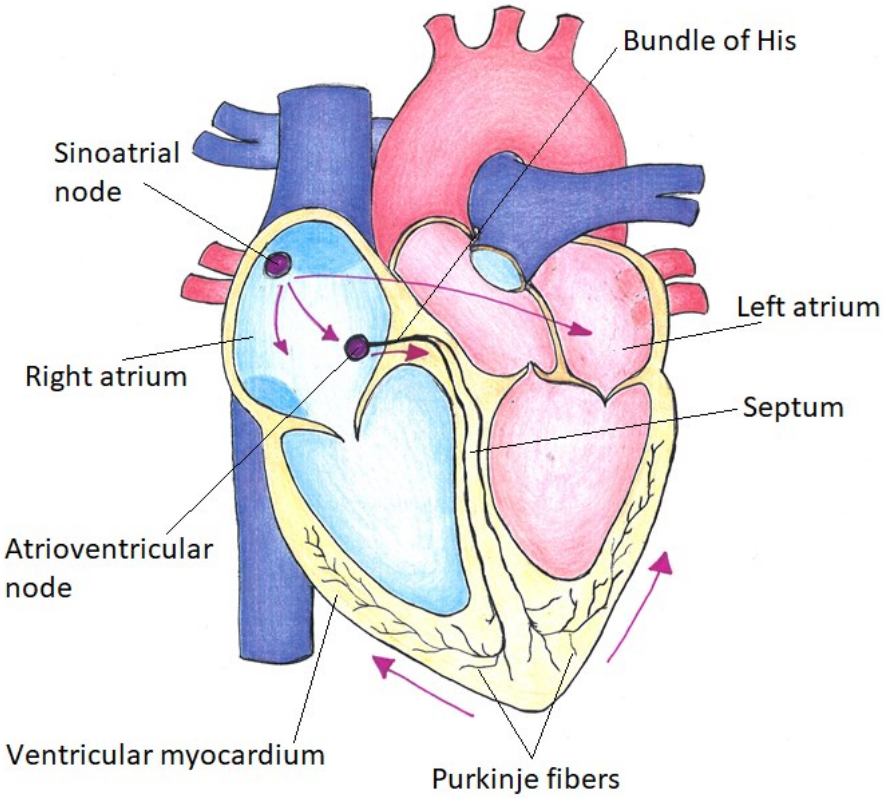

Figure 3.2. The conductive system of the heart. The pacemaker of the heart, the sinoatrial node, produces action potentials spontaneously exciting the atrioventricular node. They make atria to depolarize. Action potentials are conducted from atria via bundle of His and further Purkinje fibers to the ventricular myocardium causing the ventricles to depolarize. Arrows represent the direction of the electrical signal conduction.

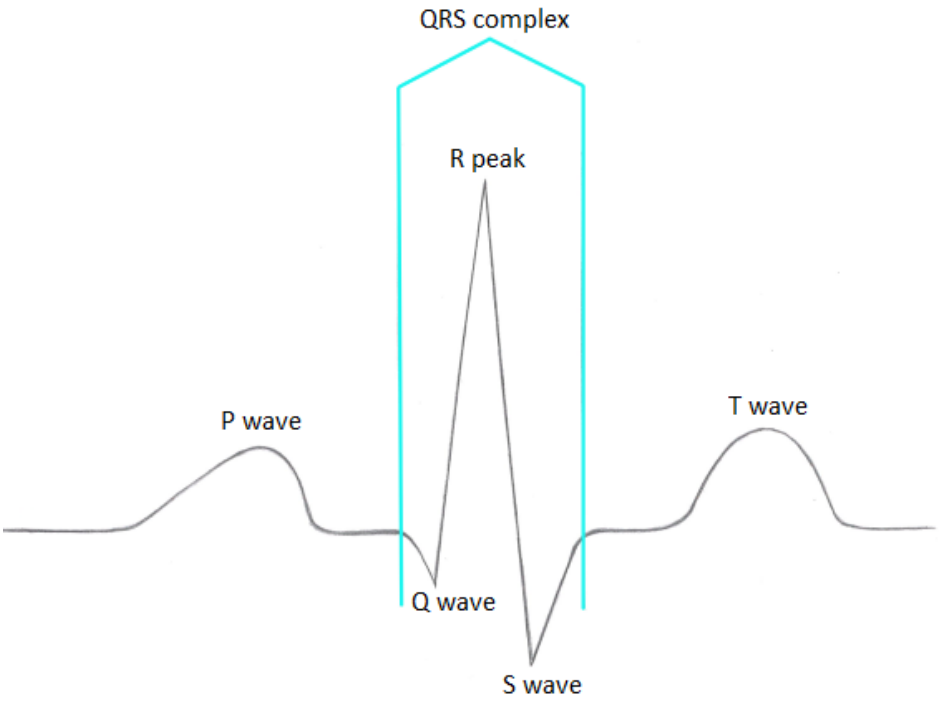

Figure 3.3. Schematic shape of one heartbeat in ECG. The depolarization of atria produces the P wave, the depolarization of ventricles generates the QRS complex and T wave is produced by the repolarization of the ventricles. Shapes and amplitudes of the waves vary between individuals and are also modulated by the lead used to record the ECG.

R peak detection

One of the several R peak detection methods is the Pan-Tompkins method [116]. At the first step of signal preprocessing, the detrended ECG signal is bandpass filtered (5 – 15 Hz) to suppress noise and power-line interference. Next, the derivative filter is applied to amplify the QRS complex and suppress the P and T waves. Third, the signal is squared. Squaring further amplifies the QRS complex and suppresses P and T waves. As the last operation of the signal processing, the moving window integrator smoothes the squared signal. The Pan-Tompkins algorithm detects the peaks of the signal, i.e. the points where the increasing signal changes its direction to decrease, from the integrated signal. After the detected beat there is about 200 ms physiological refractory period during which the ventricular depolarization cannot occur. Each detected peak is considered as a QRS complex, and to reduce the number of false QRS complexes, the dual thresholding is used to decide if the detected peak an actual QRS complex or noise. If the detected peak amplitude is under the first threshold, the noise level is updated. If the amplitude is greater than the second threshold, the detected peak is compared to the bandpass filtered signal to confirm a true QRS complex. The algorithm also searches the missed QRS complexes if there is no detected QRS complex within a period of 166 % of the mean RR interval. There is a possibility that some of the T waves are detected as QRS complexes. If there is a detected peak within 160 ms after the refractory period, it is evaluated if the peak is T wave. If the slope of the detected peak is less than half of the previous slope of the QRS complex, the peak is considered as a T wave and it is discarded. The detected QRS complexes are then used for HR determination and further HRV analyses.

3.3. HRV parameters

There are several methods for HRV assessment from which time-domain and frequency-domain measurements are the most used. Time-domain measurements assess the temporal changes in HR. Time-domain measurements can be used for all long-, short-, and ultra-short-term HRV analyses, yet the long-term Holter ECG analysis is recommended [3, 5, 117]. In time-domain measurements, HRV is determined by measuring the variation of RR intervals. Typical time-domain parameters (Table 3.2) are the mean RR interval (3.1), number of adjacent RR intervals differing more than 50 ms (RR50), the proportion of the number of adjacent RR intervals differing more than 50 ms to the total number of RR intervals (pRR50, 3.2), standard deviation (SD) of RR intervals (3.3), and root

mean square of successive differences (RMSSD, 3.4), [3, 5]. PNS and SNS contribute to SD that estimates the total variation of RR intervals [3]. It is the gold standard for cardiac risk assessment during long-term measurements, and reduced SD values predict morbidity and mortality [3]. RMSSD is used to assess the vagal effects on HRV [3].

$$RR_{av} = \frac{\sum_{i=1}^{N} RR_i}{N} \tag{3.1}$$

$$pRR50 = \frac{n_{RR50}}{N} \tag{3.2}$$

$$SD = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(RR_i - RR_{av})^2} \tag{3.3}$$

$$RMSSD = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N-1}(RR_{i+1} - RR_i)^2} \tag{3.4}$$

where RR is RR interval, RR_{av} is the mean RR interval, N is the number of the RR intervals, and n_{RR50} is the number of the successive RR intervals differing > 50 ms from each other. Time-domain parameters are often expressed as milliseconds.

Frequency-domain measurements (Table 3.2) are used to assess the dynamic changes in HR and estimate the activities of SNS and PNS. Short-term HRV measurements are preferred with frequency-domain analysis [5, 117]: more accurate results can be obtained with short-term analysis due to the ectopic beats, a greater number of artifacts, and non-stationary behavior of HR in long-term recordings [111]. However, very-low-frequency oscillations of HR may not be detected with short-term measurements [117]. Power spectral density is calculated from the HRV signal and it can be divided into four spectral ranges: ultra-low-frequency (ULF) < 0.003 Hz, very-low-frequency (VLF) < 0.04 Hz, low-frequency (LF) 0.04 – 0.15 Hz and high-frequency (HF) 0.15 – 0.4 Hz [3, 5]. The HF power reflects the PNS activity and therefore is highly correlated with RMSSD and pRR50 [3, 118]. HF range requires a minimum of 1 minute to be measured [3]. The interpretation of LF power is more complicated since it may be affected primarily by the PNS, by blood pressure regulation, or by the PNS, SNS, and blood pressure regulation together [3, 118]. Thermo- and hormonal regulation are usually the reasons for the variability within VLF power and the circadian rhythms are one probable driver of changes in ULF power requiring long-term measurements [3, 119]. The relative

activities of SNS and PNS, i.e. sympathovagal balance, can be estimated with the relation of the LF and HF powers (LF/HF): high LF/HF implies the dominance of SNS whereas low LF/HF can be interpreted as increased PNS activity [3].

Table 3.2. Time- and frequency-domain HRV parameters.

Time-domain		Frequency-domain	
RR_{AV} [ms]	Used for HR calculation	TP [ms^2]	Total variation in RR intervals
RR50	Estimation of HF HR oscillations	ULF [ms^2]	Reflects circadian rhythms
pRR50 [%]	Reflects PNS activity	VLF [ms^2]	Reflects the effects of thermal and hormonal regulation
SD [ms]	Total variation in RR intervals	LF [ms^2]	Reflects SNS and PNS activities
RMSSD [ms]	Reflects PNS activity	HF [ms^2]	Reflects PNS activity
		LF/HF	Relative SNS/PNS balance

Abbreviations: HRV = Heart rate variability, HR = Heart rate, RR_{AV} = Mean RR interval, RR50 = Number of successive RR intervals differing more than 50 ms, pRR50 = Percentage of the number of successive RR intervals differing more than 50 ms, SD = standard deviation of RR intervals, RMSSD = Root mean square of the successive RR intervals, TP = Total power, ULF = Ultra-low-frequency, VLF = Very-low-frequency, LF = Low-frequency, HF = High-frequency, SNS = Sympathetic nervous system, and PNS = Parasympathetic nervous system.

3.4. Factors affecting HRV

In addition to ANS, several other factors affect HRV. HRV has been shown to decrease with age being the highest in young adults and lowest in people over 60 years [7, 120, 121]. It has been proposed that aging-related changes in the neural system, such as the loss of neurons in the central nervous system, degrade the signal transmission and further reduce the capability to adapt to stressful situations [7, 122]. There are also differences in HRV between men and women [120, 121, 123]. Men have significantly lower parasympathetic input to cardiac regulation and higher long-term HRV than age-matched women [22, 123]. Moreover, Umetani *et al.* [120] noticed that the differences in HRV between men and women decrease with increasing age: women aged < 30 years had lower long-term HRV than men, but there were no differences in HRV between men and women over 50 years. Women had also higher HR until they were 50-years-old after which the differences between sexes disappeared [120]. Hormonal regulation may partly explain the differences in HRV between men and women. Postmenopausal women with estrogen replacement therapy have been shown to have higher HRV than women without it [124]. Estrogen has also been shown to decrease the SNS

regulation and increase the PNS regulation elevating the high-frequency HRV [125]. Moreover, wakefulness, sleep, and sleep stages affect the HRV [8, 126–129].

During wakefulness, SNS is dominant, but when passing from wakefulness to NREM, the proportion of PNS activity is increased [8]. NREM sleep is characterized by prevailed PNS and reduced SNS activities leading to decreased HR and thus increased HRV [8, 126]. HRV is also observed to gradually increase from N1 to N3 in NREM [127]. In REM, the SNS activity increases markedly compared to NREM increasing the HR and decreasing HRV [8, 126]. Yet, the SNS activity is reduced in REM compared to wakefulness [8]. Moreover, arousals related to respiratory events activate the sympathetic nervous system (SNS) decreasing the HRV [128].

In OSA, the sympathetic tone is elevated. Respiratory events, i.e. apneas and hypopneas, cause intermittent blood oxygen desaturations that lead to hypoxemia and hypercapnia and further intrathoracic pressure swings and cortical arousals from sleep [9–11]. During the respiratory event, HR decreases, but at the resumption of breath, the HR increases abruptly [130]. This is called cyclical heart rate variation. In addition, intermittent hypoxia elevates the chemosensitivity of the carotid body [131]. Together these factors activate SNS and lead to cyclical changes in HR and reduced long-term HRV. Low nocturnal blood pressure is thought to protect the normal functioning of the cardiac system, but in OSA patients, the intermittent SNS activation elevates the blood pressure during sleep [8] leading to elevated risk for hypertension [14, 24, 89]. Moreover, this increases the risk for, and may even cause, cardiovascular diseases [8]. Together with hypoxemia, hypercapnia, and elevated SNS activity, pulmonary hypertension and negative intrathoracic pressure increase the risk for arrhythmias in OSA patients [11, 12, 91]. The relative risk for nocturnal arrhythmias is increased nearly 18-fold within 90 s after the end of the respiratory event in OSA [92]. Furthermore, increased SNS activity can also cause oxidative stress, systemic inflammation, and vascular dysfunction [11] leading to possible structural and electrical cardiac remodeling in the long run [12]. In addition to increased risk for hypertension and arrhythmias, these changes elevate the risk for heart failure [132] and stroke [13].

4. Aims and hypotheses of the study

Low long-term HRV is a significant risk factor for several health consequences such as cardiovascular diseases [7]. It has been shown that OSA patients have reduced long-term HRV [15, 16] and that they have the shorter RR intervals the more severe OSA is [17]. It has also been observed that the decrease in RR intervals after apneas increase with increasing apnea duration, but the population in this study included only 8 patients [18]. Thus, larger and more comprehensive research is required to investigate the link between the respiratory event duration and HRV. Furthermore, the effect of the respiratory event type on HRV is rarely studied. Men are observed to have significantly higher long-term HRV and lower parasympathetic input to cardiac regulation compared to age-matched women albeit they have a higher risk for cardiovascular diseases [22]. Men also tend to have more severe OSA with longer respiratory events compared to women [10]. Thus, it is evident that men and women should be studied separately when investigating the connection between OSA and HRV.

Therefore, this Master thesis aimed to study whether the sex and the respiratory event type and duration affect ultra-short-term HRV and the changes in RR interval during and after respiratory events. Consequently, this thesis hypothesized that 1) longer respiratory events are related to an elevated ultra-short-term HRV due to pronounced RR interval prolonging during and shortening after apneas and hypopneas, 2) apneas cause higher ultra-short-term HRV and a greater decrease in RR intervals after the event and 3) these phenomena are stronger in men compared to women.

5. Methods

The dataset used in this Master thesis was collected between 2015 and 2017 at the Princess Alexandra Hospital (Brisbane, Australia). The Institutional Human Research Ethics Committee of the Princess Alexandra Hospital approved the data collection (HREC/16/QPAH/021 and LNR/2019/QMS/54313). Full diagnostic PSG was conducted for 892 patients due to the clinical suspicion of OSA using the Compumedics Grael acquisition system (Compumedics, Abbotsford, Australia). The recordings were scored manually by ten experienced scorers who participate regularly in intra- and inter-laboratory scoring concordance activities. According to the prevalent AASM scoring criteria [2], the respiratory event was scored as apnea if there is complete breathing cessation for ≥ 10 seconds during which the airflow is decreased ≥ 90 %. The respiratory event was scored as hypopnea if the airflow is partially decreased (≥ 30 %) for ≥ 10 seconds and the event is associated with arousal or there is a ≥ 3 % oxygen desaturation from the baseline before the respiratory event [2].

The scored PSGs were retrospectively utilized in this study. 30 patients, who had incomplete demographic data or did not have any respiratory events, were excluded. Therefore, PSGs of 862 suspected OSA patients were included in the final dataset, of which 473 (54.9 %) were men. Information about comorbidities was collected from the medical records of the patients and the demographic data is presented in Table 5.1.

The nocturnal ECGs were recorded as a part of PSG using lead II placement with a sampling frequency of 256 Hz [2]. ECG detrending was performed with the smoothness priors method with a smoothing parameter λ value of 500 [133] and subsequently, R peaks were detected from the ECGs with the Pan-Tompkins method (Chapter 3.2). The bandpass filtering required in the first phase of the Pan-Tompkins method was executed with high- and low-pass Kaiser-window finite impulse response (FIR) filters with the cut-off frequencies of 5 Hz and 15 Hz, respectively. ECG pre-processing and a time-domain HRV analysis were performed with the Signal Processing Toolbox of MATLAB R2018b (MathWorks Inc, MA, USA).

Table 5.1. Characteristics of suspected obstructive sleep apnea (OSA) patients. Continuous variables are presented as a median (interquartile range) and discrete variables as a count (percentage).

	All	***Men***	***Women***
Number of patients	862 (100 %)	473 (54.9 %)	389 (45.1 %)
No OSA (AHI < 5)	140 (16.2 %)	47 (9.9 %)	93 (23.9 %) †
Mild OSA (5 ≤ AHI < 15)	271 (31.4 %)	126 (26.6 %)	145 (37.3 %) †
Moderate OSA (15 ≤ AHI < 30)	205 (23.8 %)	127 (26.8 %)	78 (20.1 %) †
Severe OSA (AHI ≥ 30)	246 (28.5 %)	173 (36.6 %)	73 (18.8 %) †
Number of events			
All	44414	27581	16833
Apneas	8848	6576	2272
10 – 20 s	2956 (33.4 %)	1907 (29.0 %)	1049 (46.2 %) †
20 – 30 s	3156 (35.7 %)	2443 (37.2 %)	713 (31.4 %) †
> 30 s	2736 (30.9 %)	2226 (33.9 %)	510 (22.5 %) †
Hypopneas	35566	21005	14561
10 – 20 s	13898 (39.1 %)	7284 (34.7 %)	6614 (45.4 %) †
20 – 30 s	11529 (32.4 %)	7065 (33.6 %)	4464 (30.7 %) †
> 30 s	10139 (28.5 %)	6656 (31.7 %)	3483 (23.9 %) †
Event duration [s]			
All	23.1 (17.0, 31.8)	24.4 (17.9, 33.1)	21.1 (15.7, 29.4) *
Apneas	24.3 (17.8, 32.1)	25.5 (18.9, 33.1)	20.8 (15.8, 28.8) *
Hypopneas	22.7 (16.8, 31.7)	24.0 (17.6, 33.2)	21.1 (15.7, 29.5) *
AHI [events/h]	15.8 (7.0, 32.6)	22.1 (10.4, 40.5)	11.5 (5.1, 21.8) *
$ODI_{3\%}$ [desaturations/h]	16.4 (5.1, 39.3)	21.5 (7.6, 46.5)	10.5 (3.7, 29.1) *
Total sleep time [min]	309.5 (254.5, 360.0)	294.0 (249.5, 352.9)	323.0 (267.4, 367.5) *
Age [y]	55.9 (44.7, 65.8)	57.0 (45.4, 67.1)	54.1 (44.0, 64.1) *
BMI [kg/m^2]	34.5 (29.4, 40.4)	33.1 (28.7, 38.7)	36.2 (30.7, 43.0) *
Comorbidities			
Atrial Arrhythmia	91 (10.6 %)	70 (14.8 %)	21 (5.4 %) †
Cardiac Failure	19 (2.2 %)	10 (2.1 %)	9 (2.3 %)
Diabetes Mellitus, type 1	6 (0.7 %)	4 (0.8 %)	2 (0.5 %)
Diabetes Mellitus, type 2	184 (21.3 %)	102 (21.6 %)	82 (21.1 %)
Hypertension	360 (41.8 %)	208 (44.0 %)	152 (39.1 %)
Smokers	139 (16.1 %)	79 (16.7 %)	60 (15.4 %)

Information about comorbidities was collected from the medical records of patients. Abbreviations: BMI = Body mass index, AHI = Apnea-hypopnea index, $ODI_{3\%}$ = Oxygen desaturation index according to AASM 2012 scoring criteria (desaturation ≥ 3 %).

* = Statistically significant difference ($p < 0.05$) compared to men according to the Mann-Whitney *U* test.

† = Statistically significant difference ($p < 0.05$) compared to men according to χ^2-test.

For each scored apnea and hypopnea, in- and post-event segments were extracted from the ECG signal. The in-event segment was defined based on the start- and endpoints of the respiratory event and the post-event segment was the 15-second period immediately after the end of the respiratory event. Post-event segment duration of 15 seconds was chosen to achieve a reliable representation of temporal changes in RR intervals: longer period would have limited the number of respiratory events excessively whereas shorter period would have not left enough time for RR intervals to be restored to level before the respiratory event. Respiratory events with overlapping post- and in-event segments were excluded as well as the events that were closer than 15 seconds to the end of the ECG registration. These criteria excluded a total of 69 675 respiratory events. A total of 44 414 respiratory events were included for a further analysis, of which 8 848 were apneas and 35 566 hypopneas. Apneas and hypopneas were studied separately in three subgroups based on their duration (10 – 20 s, 20 – 30 s, and > 30 s). Moreover, the following HRV analysis was conducted separately for men and women.

Typical time-domain HRV parameters were computed for each ECG segment. These parameters included RR intervals, RR_{AV}, SD, RMSSD, and pRR50 [3]. The time-domain HRV parameters are more suitable for ultra-short-term HRV analysis, and thus they were chosen over frequency-domain parameters [3, 4]. The difference between in- and post-event RR intervals was calculated by subtracting the mean post-event RR interval from the mean in-event RR interval (5.1).

$$\Delta RR_{AV} = RR_{AV}^{In} - RR_{AV}^{Post} \tag{5.1}$$

where ΔRR_{AV} is the change in mean RR interval, RR_{AV}^{In} is the mean in-event RR interval and RR_{AV}^{Post} is the mean post-event RR interval. The relative changes in post-event HRV parameter values compared to in-event values were calculated by subtracting the median in-event parameter value from the median post-event value and dividing it by the median in-event value (5.2).

$$\Delta HRV_{Rel} = \frac{HRV^{Post} - HRV^{In}}{HRV^{In}} * 100\% \tag{5.2}$$

where ΔHRV_{Rel} is the relative change between in- and post-event HRV parameter values (SD, RMSSD, or pRR50), HRV^{Post} and HRV^{In} are the in- and post-event HRV parameter values, respectively.

Chi-squared (χ^2) test was used to test the statistical difference between the discrete demographic parameters of men and women (Table 5.1). The Wilcoxon signed-rank test was used to test the statistical significance of the difference between in- and post-event RR intervals and between other in- and post-event ultra-short-term HRV parameters. The statistical significance of the difference between the respiratory event duration-based subgroups was tested separately for apneas and hypopneas with the Mann-Whitney *U* test. All statistical tests were performed with Statistics and Machine Learning Toolbox of MATLAB R2018b.

The RR interval signals during and after respiratory events were detrended using the smoothness priors method ($\lambda = 500$) [133] and further spline interpolated for illustrative reasons. Due to about 200 ms refractory period of the myocardial cells, the interpolated values of RR intervals under 200 ms were excluded [116]. Finally, median RR intervals were plotted as a function of time separately for apneas, hypopneas, men, and women.

6. Results

6.1. HRV in men

In apneas, the mean in-event RR interval increased, and the mean post-event RR interval shortened with increasing apnea duration ($p < 0.05$, Table 6.1). Furthermore, the in-event SD, RMSSD, and pRR50 were observed to increase as the apnea duration increased ($p < 0.05$, Table 6.1). The post-event values of SD, RMSSD, and pRR50 of 20 – 30 s and > 30 s apneas were greater than those of 10 – 20 s apneas ($p < 0.05$, Table 6.1). However, there were no significant differences between 20 – 30 s and > 30 s apneas (Table 6.1).

Table 6.1. In- and post-event time-domain heart rate variability (HRV) parameter values for men and women based on the apnea duration.

	In-event			**Post-event**		
	Men	**Women**	**p-value**	**Men**	**Women**	**p-value**
10 – 20 s						
Mean RR Interval [s]	0.961	0.927	**0.025**	0.889	0.889	0.221
SD [ms]	34	31	**0.009**	47	40	**< 0.001**
RMSSD [ms]	22	24	**0.038**	32	32	0.846
pRR50 [%]	0.0	5.3	0.757	11.8	11.8	0.597
20 – 30 s						
Mean RR Interval [s]	0.960	1.005*	**< 0.001**	0.881*	0.911*	**< 0.001**
SD [ms]	49*	41*	**< 0.001**	60*	47*	**< 0.001**
RMSSD [ms]	31*	34*	0.837	37*	38*	0.757
pRR50 [%]	10.0*	11.1*	0.665	15.8*	15.4*	0.300
> 30 s						
Mean RR Interval [s]	0.970*†	0.932*†	0.055	0.858*†	0.852*†	0.636
SD [ms]	61*†	49*†	**< 0.001**	58*	46*	**0.001**
RMSSD [ms]	40*†	36*	**0.001**	39*	31†	**< 0.001**
pRR50 [%]	12.0*†	12.3*	0.544	15.8*	11.1†	**< 0.001**

Parameter medians were calculated from ECG recorded during apneas (in-event) and the 15 seconds immediately after the apneas (post-event). The *p*-values in the table represent the statistical significance of the differences between men and women based on the Mann-Whitney *U* test; bolded *p*-values indicate statistical significance ($p < 0.05$). Abbreviations: SD = standard deviation, RMSSD = root mean square of successive differences, pRR50 = the number of adjacent RR intervals differing more than 50 ms divided by the total number of RR intervals during the apnea.

* = statistically significant difference ($p < 0.05$, the Mann-Whitney *U* test) compared to the 10-20 s apneas.

† = statistically significant difference ($p < 0.05$, the Mann-Whitney *U* test) compared to the 20-30 s apneas.

Similarly, in hypopneas, the mean in-event RR interval increased, and the post-event RR interval shortened with increasing hypopnea duration ($p < 0.05$, Table 6.2). The in-event SD, RMSSD, and pRR50 were observed to increase significantly as the hypopnea duration increased ($p < 0.05$, Table 6.2). Furthermore, the post-event SD, RMSSD, and pRR50 were greater in 20 – 30 s and > 30 s hypopneas when compared to the 10 – 20 s hypopneas ($p < 0.05$, Table 6.2).

Table 6.2. In- and post-event time-domain heart rate variability (HRV) parameter values for men and women based on the hypopnea duration.

	In-event			**Post-event**		
	Men	**Women**	***p*-value**	**Men**	**Women**	***p*-value**
10 – 20 s						
Mean RR Interval [s]	0.913	0.866	**< 0.001**	0.865	0.833	**< 0.001**
SD [ms]	31	26	**< 0.001**	41	33	**< 0.001**
RMSSD [ms]	26	23	**< 0.001**	29	25	**< 0.001**
pRR50 [%]	5.9	0.0	**< 0.001**	7.1	5.3	**< 0.001**
20 – 30 s						
Mean RR Interval [s]	0.960*	0.900*	**< 0.001**	0.901*	0.855*	**< 0.001**
SD [ms]	39*	31*	**< 0.001**	46*	38*	**< 0.001**
RMSSD [ms]	31*	26*	**< 0.001**	33*	27*	**< 0.001**
pRR50 [%]	9.4*	5.0*	**< 0.001**	11.8*	6.3*	**< 0.001**
> 30 s						
Mean RR Interval [s]	0.987*†	0.892*†	**< 0.001**	0.903*	0.834†	**< 0.001**
SD [ms]	47*†	34*†	**< 0.001**	48*†	37*	**< 0.001**
RMSSD [ms]	37*†	26*	**< 0.001**	34*	25†	**< 0.001**
pRR50 [%]	11.9*†	5.0*	**< 0.001**	12.5*	5.6†	**< 0.001**

Parameter medians were calculated from ECG recorded during hypopneas (in-event) and the 15 seconds immediately after the hypopneas (post-event). The *p*-values in the table represent the statistical significance of the differences between men and women based on the Mann-Whitney *U* test; bolded *p*-values indicate statistical significance ($p < 0.05$). Abbreviations: SD = standard deviation, RMSSD = root mean square of successive differences, pRR50 = the number of adjacent RR intervals differing more than 50 ms divided by the total number of RR intervals during the hypopnea.

* = Statistically significant difference ($p < 0.05$, the Mann-Whitney *U* test) compared to the 10-20 s hypopneas.

† = Statistically significant difference ($p < 0.05$, the Mann-Whitney *U* test) compared to the 20-30 s hypopneas.

Regardless of the apnea duration, the post-event RR intervals were significantly shorter compared to the in-event RR intervals ($p < 0.001$, Table 6.1). The same phenomenon was observed in hypopneas ($p < 0.001$, Table 6.2). In addition, the difference between in- and post-event RR intervals increased with increasing respiratory event duration in both apneas ($p < 0.001$, Table 6.3, Figure 6.1) and hypopneas ($p < 0.001$, Table 6.3, Figure 6.2). Moreover, the relative change between in- and

post-event HRV parameters decreased as the duration of apneas increased ($p < 0.001$, Table 6.4). Also in hypopneas, the relative change between in- and post-event HRV parameters decreased with increasing hypopnea duration ($p < 0.05$), except the difference between relative pRR50 changes of 10 – 20 s and 20 – 30 s hypopneas was not significant (Table 6.4).

Table 6.3. The median differences [s] between in- (i.e. during the event) and post-event (i.e. 15 seconds after the event) RR intervals in different respiratory event duration groups.

	Apneas			Hypopneas		
	Men	**Women**	***p*-value**	**Men**	**Women**	***p*-value**
10 – 20 s	0.047	0.030	**< 0.001**	0.031	0.022	**< 0.001**
20 – 30 s	0.068	0.070	0.391	0.044	0.031	**< 0.001**
> 30 s	0.096	0.087	**0.030**	0.059	0.042	**< 0.001**

p-values presented in the table denote the statistically significant difference in the median RR interval between men and women (the Mann-Whitney *U* test). Statistically significant *p*-values ($p < 0.05$) are bolded. All median differences between in- and post-event RR intervals were significant ($p < 0.001$) according to Wilcoxon signed-rank test and all the differences between event duration derived groups were significant ($p < 0.001$) according to the Mann-Whitney *U* test.

Table 6.4. The relative changes [%] between in- (i.e. during the event) and post-event (i.e. 15 seconds after the event) HRV parameters in different respiratory event duration groups.

	Apneas			Hypopneas		
	Men	**Women**	***p*-value**	**Men**	**Women**	***p*-value**
10 – 20 s						
ΔSD_{Rel}	39.7	31.3	**< 0.001**	33.0	29.5	**< 0.001**
$\Delta RMSSD_{Rel}$	43.6	32.5	**< 0.001**	11.9	6.1	**< 0.001**
$\Delta pRR50_{Rel}$	NaN	123.5	**0.008**	21.4	NaN	0.067
20 – 30 s						
ΔSD_{Rel}	22.9*	13.1	**< 0.001**	19.7*	21.8*	**< 0.001**
$\Delta RMSSD_{Rel}$	18.8*	13.4	**< 0.001**	5.5*	4.4*	**< 0.001**
$\Delta pRR50_{Rel}$	57.9*	38.5*	**< 0.001**	25.5	25.0	0.316
> 30 s						
ΔSD_{Rel}	-6.1*†	-6.4*†	**< 0.001**	1.8*†	9.8*†	**< 0.001**
$\Delta RMSSD_{Rel}$	-3.1*†	-11.9*†	**< 0.001**	-8.3†	-3.6*†	**< 0.001**
$\Delta pRR50_{Rel}$	31.6*†	-9.3*†	0.306	5.0*†	11.1*†	0.945

p-values presented in the table denote the statistically significant relative difference in HRV parameters between men and women (the Mann-Whitney *U* test). Statistically significant *p*-values ($p < 0.05$) are bolded. Abbreviations: HRV = heart rate variability, SD = standard deviation, RMSSD = root mean square of successive differences, pRR50 = the number of adjacent RR intervals differing more than 50 ms divided by the total number of RR intervals during the hypopnea, NaN = not a number due to the divisor, the in-event HRV parameter, being zero in equation (5.2).

* = Statistically significant difference compared to the 10-20 s events (apneas: $p < 0.001$, hypopneas: $p < 0.05$, the Mann-Whitney *U* test).

† = Statistically significant difference compared to the 20-30 s events (apneas: $p < 0.001$, hypopneas: $p < 0.05$, the Mann-Whitney *U* test).

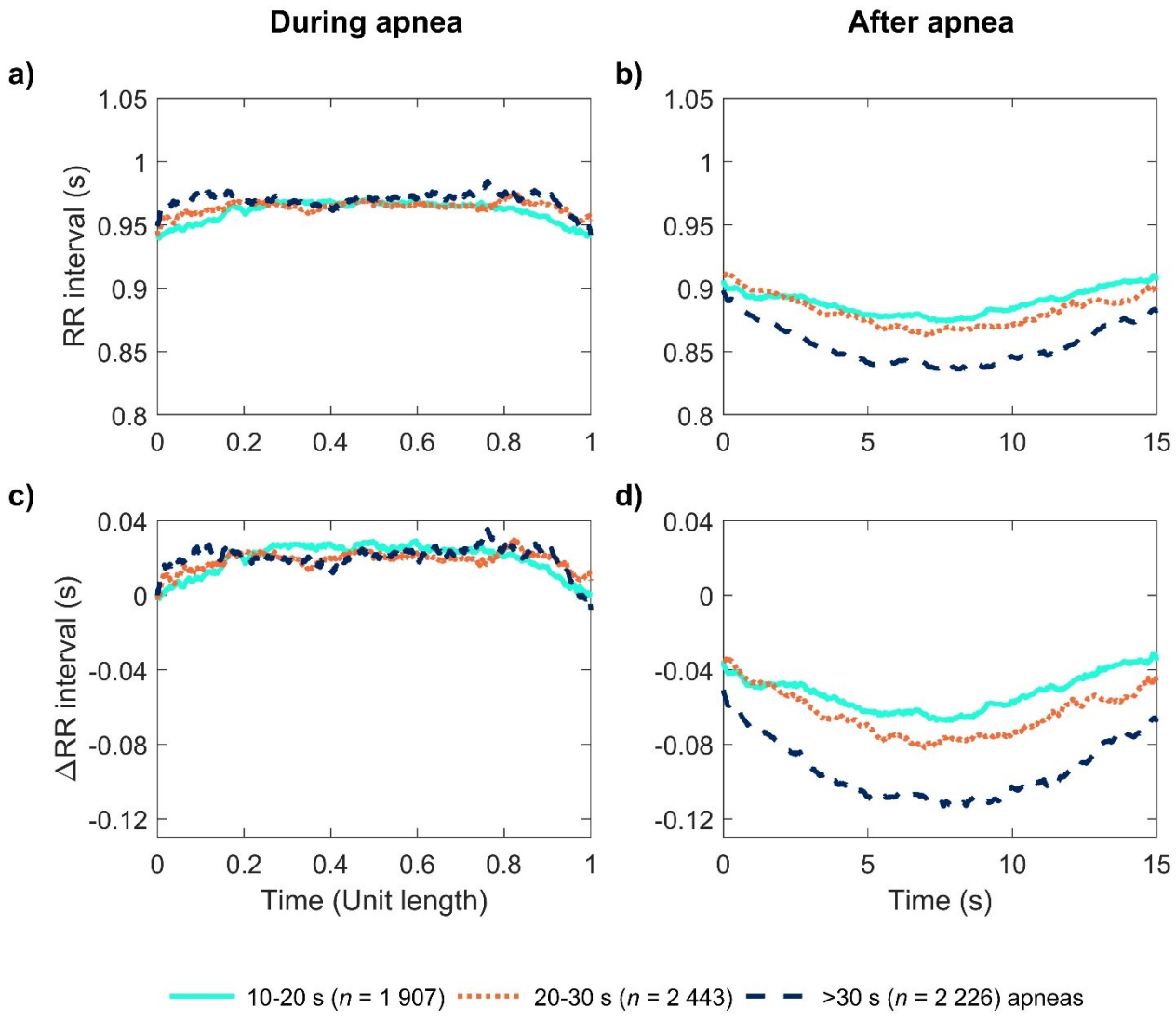

Figure 6.1. RR intervals related to apneas (*n* = 6 576) of men (*N* = 381). In-event RR intervals (during apnea) are presented in a subfigure **a)** and post-event RR intervals (immediately after apnea) are shown in subfigure **b)**. In subfigures **c)** and **d)** are the absolute RR interval changes relative to the beginning of the apnea during and after the event, respectively. The duration of each apnea is normalized to 1 in subfigures **a)** and **c)**.

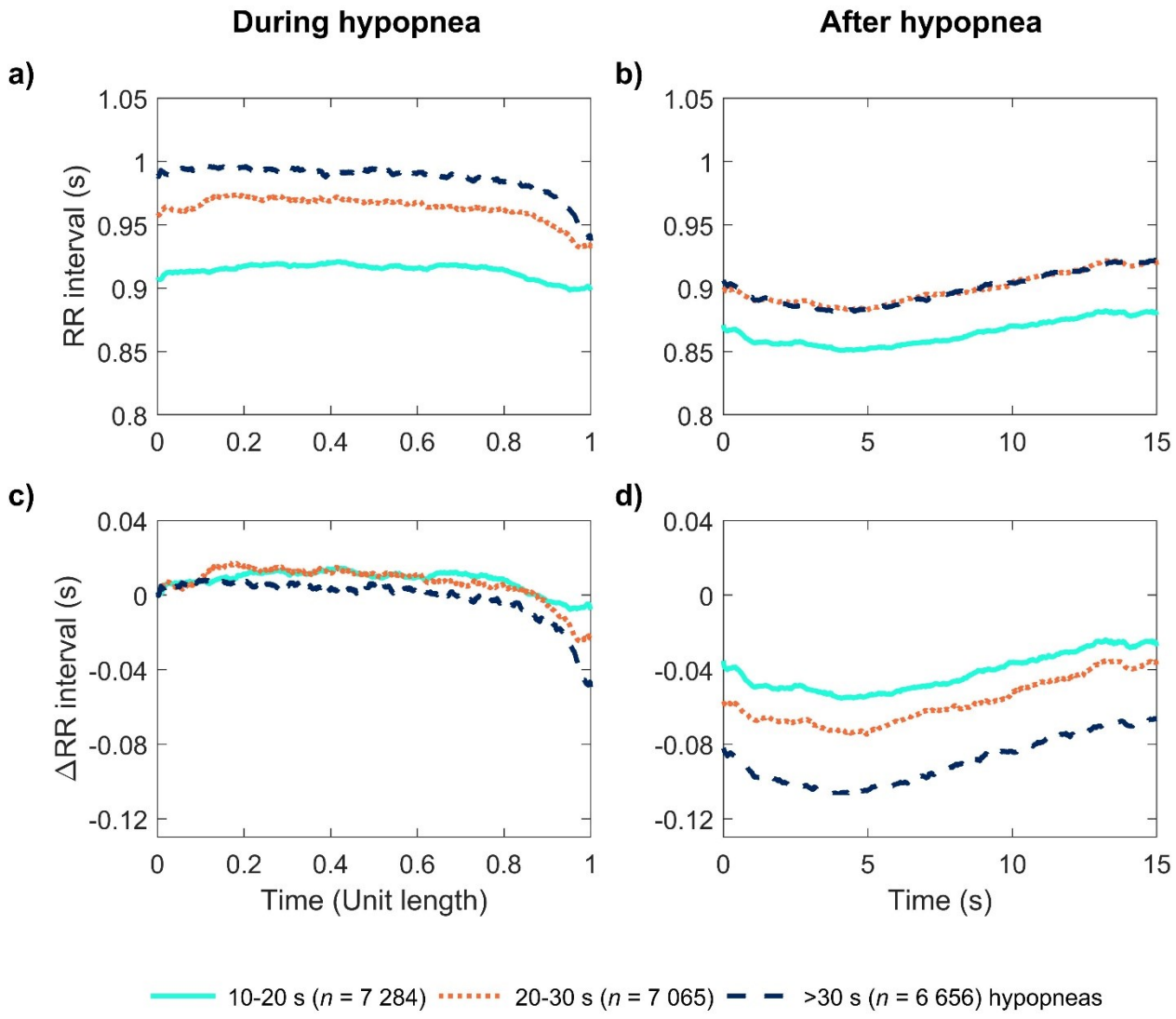

Figure 6.2. RR intervals related to hypopneas (*n* = 21 005) of men (*N* = 472). In-event RR intervals (during hypopnea) are presented in a subfigure **a)** and post-event RR intervals (immediately after hypopnea) are shown in subfigure **b)**. In subfigures **c)** and **d)** are the absolute RR interval changes relative to the beginning of the hypopnea during and after the event, respectively. The duration of each hypopnea is normalized to 1 in subfigures **a)** and **c)**.

6.2. HRV in women

The in-event SD, RMSSD, and pRR50 were significantly greater in apneas of 20 – 30 s and > 30 s apneas than in 10 – 20 s ($p < 0.05$, Table 6.1). However, the post-event HRV parameters were observed to be greatest in 20 – 30 s apneas: the post-event mean RR intervals, RMSSD, and pRR50 were significantly higher in 20 – 30 s apneas compared to apneas of 10-20 s and >30 s ($p < 0.05$, Table 6.1).

In hypopneas, the in-event SD values were observed to increase significantly as the hypopnea duration increased ($p < 0.05$, Table 6.2). The in-event RMSSD and pRR50 values of 20 – 30 s and > 30 s hypopneas were greater compared to 10 – 20 s hypopneas ($p < 0.05$, Table 6.2). Between hypopneas of 20 – 30 s and > 30 s, however, there were insignificant differences in these parameters (Table 6.2). When compared to 10 – 20 s and > 30 s hypopneas, 20 – 30 s hypopneas had the highest post-event RMSSD and pRR50 values ($p < 0.05$, Table 6.2).

In both apneas and hypopneas, the median in- and post-event RR intervals were the longest in 20 – 30 s respiratory events ($p < 0.001$, Tables 6.2 and 6.3). Furthermore, the post-event RR intervals were significantly shorter compared to the in-event RR intervals ($p < 0.001$, Tables 6.2 and 6.3) and the median difference between the in- and post-event RR intervals increased as the respiratory event duration increased in both apneas and hypopneas ($p < 0.001$, Table 6.3, Figures 6.3 and 6.4). Furthermore, the relative change in post-event HRV parameter values compared to in-event values was generally more substantial in shorter apneas and hypopneas (apneas: $p < 0.001$, hypopneas: $p < 0.05$, Table 6.4).

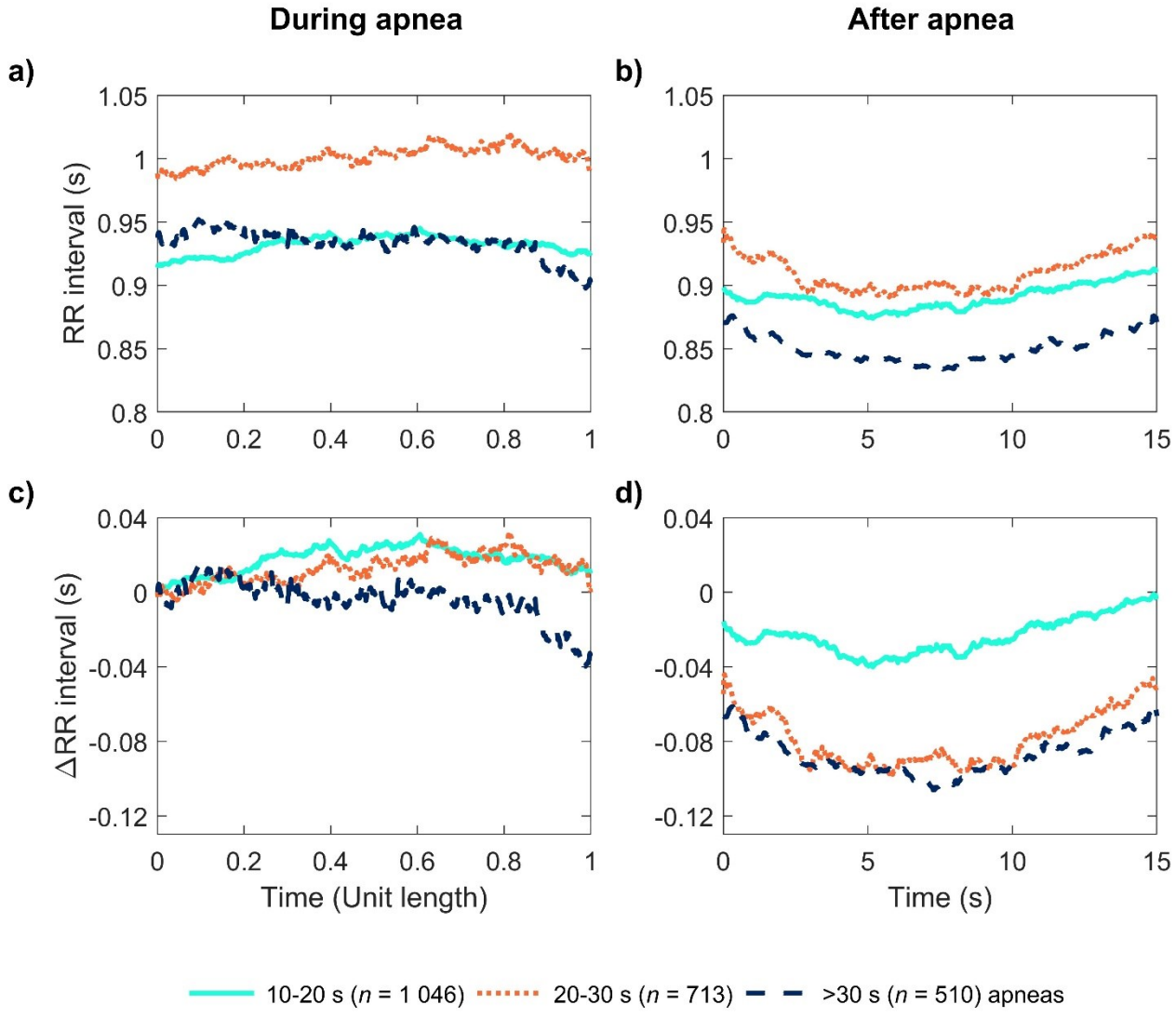

Figure 6.3. RR intervals related to apneas (*n* = 2 272) of women (*N* = 254). In-event RR intervals (during apnea) are presented in a subfigure **a)** and post-event RR intervals (immediately after apnea) are shown in subfigure **b)**. In subfigures **c)** and **d)** are the absolute RR interval changes relative to the beginning of the apnea during and after the event, respectively. The duration of each apnea is normalized to 1 in subfigures **a)** and **c)**.

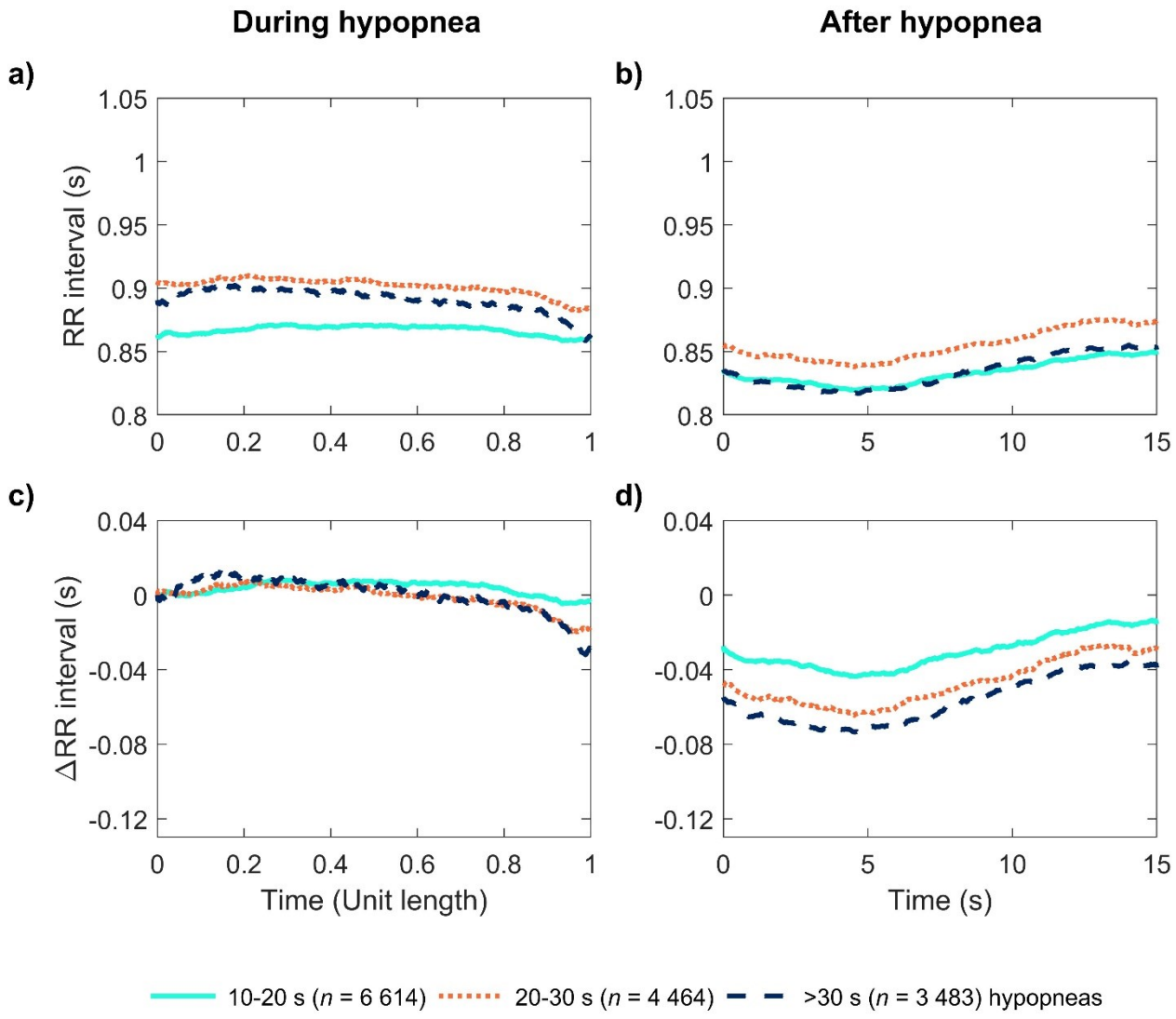

Figure 6.4. RR intervals related to hypopneas (*n* = 14 561) of women (*N* = 386). In-event RR intervals (during hypopnea) are presented in a subfigure **a)** and post-event RR intervals (immediately after hypopnea) are shown in subfigure **b)**. In subfigures **c)** and **d)** are the absolute RR interval changes relative to the beginning of the hypopnea during and after the event, respectively. The duration of each hypopnea is normalized to 1 in subfigures **a)** and **c)**.

6.3. Differences in HRV parameters

54.9 % of the study population were men (Table 5.1). They were significantly ($p < 0.05$) older and had a lower BMI than women. They were also more frequently diagnosed with atrial arrhythmias compared to women ($p < 0.05$). Otherwise, no statistically significant differences were observed between sexes in the existence of comorbidities. Men were diagnosed to have moderate or severe OSA more often and they also had more severe OSA (AHI, ODI, respiratory event duration) compared to women ($p < 0.05$).

All HRV parameters of hypopneas were observed to be significantly higher in men compared to women ($p < 0.001$, Table 6.2). In apneas, the in- and post-event SD were greater in men than in women ($p < 0.05$, Table 6.1). The RMSSD and pRR50 values of men were generally equal to or smaller than those of women, but these differences were statistically insignificant ($p > 0.05$, Table 6.1). Moreover, women had greater, but insignificant, difference between in- and post-event RR intervals in 20 – 30 s apneas ($p > 0.05$), but otherwise, the differences were greater in men compared to women ($p < 0.05$, Table 6.3). Moreover, men had greater relative changes between in- and post-event SD and RMSSD ($p < 0.05$), but the differences in relative changes of pRR50 between men and women were mainly insignificant ($p > 0.05$, Table 6.4).

7. Discussion

The main purpose of this study was to investigate whether the respiratory event duration and type modulate the changes in ultra-short-term HRV and RR intervals and whether the sex affects these changes. This was done by comparing the median difference of in- and post-event RR interval values and the time-domain HRV parameter values of suspected OSA patients (*n* = 862) between respiratory events having a different duration and type. These analyses were performed separately for men and women. In ultra-short-term HRV analysis, it was observed that longer respiratory events are associated with increased HRV and a greater decrease between in- and post-event RR intervals. Furthermore, higher ultra-short-term HRV and greater differences between in- and post-event RR intervals were more strongly related to apneas and men.

It was hypothesized that the longer respiratory events are associated with a greater decrease in the post-event RR interval after the respiratory event. The results of this study are in line with this hypothesis: the median difference in RR interval was the greater the longer the related apnea or hypopnea was in both men and women (Table 6.3). Similar results have been obtained from previous studies. The respiratory events are associated with cyclical heart rate variation, i.e. slowing down of HR (bradycardia) during and quickening of HR (tachycardia) after the respiratory event [130]. Moreover, longer apneas have been shown to cause greater bradycardia [134] and a greater decrease in RR intervals after the respiratory event [18]. These differences may be explained by the degree of oxygen desaturation (desaturation severity). Kulkas *et al.* [19] observed in their study that longer apneas and hypopneas are associated with more severe desaturations. The deeper desaturations lead to more severe hypoxia, hypercapnia, and SNS activation, all being risk factors for arrhythmias [11, 12]. While apneas and hypopneas are rarely considered separately [18, 130, 134], Chouchou *et al.* [135] showed that the respiratory event duration and type do not significantly decrease the RR interval duration after the respiratory event. This is, however, in disagreement with several other studies that have shown the respiratory event duration and type affecting the physiological consequences, e.g. blood pressure, the depth of the oxygen desaturations and arousal from sleep, [19, 136–138], that are known to be linked with the increase in HR, i.e. RR interval shortening. Their finding may be a consequence of their small size of the studied population (*n* = 16). Thus, more detailed clarification on the link between HRV and desaturations requires further research.

It was also hypothesized that ultra-short-term HRV increases with increasing respiratory event duration. Supporting this hypothesis, the ultra-short-term HRV generally increased as the apnea and hypopnea duration increased. The relative change between in- and post-event HRV parameters, however, was more substantial in shorter respiratory events. The chemosensitivity of the carotid body is increased by long-term intermittent hypoxia causing elevated SNS activity, HR, and reduced long-term HRV [131]. Moreover, the arousal threshold of shorter respiratory events is decreased compared to longer events, i.e. shorter events end with arousal more often, causing sleep fragmentation and they are linked to elevated mortality in both sexes [47, 139]. In addition, OSA increases significantly the risk for arrhythmias [12, 92]. It could, therefore, be useful to consider the characteristics of respiratory events and ultra-short-term HRV in OSA diagnostics when estimating the OSA-related cardiac consequences. However, the results of this thesis did not consider the severity markers of OSA, e.g. the AHI of the patients or inter-individual variation. SNS and PNS regulation is individual and thus, further research on the combined effect of OSA severity and the duration of respiratory events on HRV is warranted.

Supporting the hypotheses, differences between in- and post-event RR intervals were greater in apneas compared to hypopneas regardless of the sex (Table 6.3). Moreover, apneas caused also a significantly greater ultra-short-term HRV (Tables 6.1 and 6.2). The minimum RR interval value was reached approximately 4 s after the hypopnea termination (Figures 6.2 and 6.4), whereas in apneas the minimum was reached later, approximately 7 s after the apnea termination (Figures 6.1 and 6.3). It has been shown that apneas are responsible for more severe oxygen desaturations [19] that increase the risk for cardiovascular diseases [20, 21]. OSA patients have been shown to have increased probability of cardiogenic sudden deaths between midnight and 6 a.m. [140] and similarly, the frequency and severity of respiratory events are known to increase towards morning [60]. It has also been observed that the risk of arrhythmia is nearly 18-fold within 90 s after respiratory event termination [92]. The increased tendency for arrhythmias in OSA patients has been explained with elevated SNS activity, negative intrathoracic pressure, and hypertension [91]. Albeit bad health outcomes are commonly associated with low long-term HRV [132, 141], high ultra-short-term HRV may be more damaging due to increased RR interval variation within a relatively short time. For example, it could be that arrhythmias induced by respiratory events affect the ultra-short-term HRV by increasing it. With earlier findings [19–21, 60, 91, 92, 140] the results of this thesis indicate that the cardiac regulation is modulated by the type of respiratory events, possibly due to different

proportions of SNS and PNS activations. Besides AHI, detailed ECG and HRV analysis could be beneficial when estimating the risk for cardiovascular events in OSA severity evaluation, especially in the case of patients with cardiovascular comorbidities.

In hypopneas, men had significantly greater values of all ultra-short-term HRV parameters than women (Table 6.2). However, the differences between HRV parameters of men and women related to apneas had more variation (Table 6.1). In apneas, men had greater in- and post-event SD values than women. Moreover, men had generally lower or equal RMSSD and pRR50 values compared to those of women, but these differences were statistically insignificant. Furthermore, men had generally greater differences between in- and post-event RR intervals (Table 6.3) and greater relative changes between in- and post-event HRV parameters (Table 6.4). Long-term HRV has shown to be significantly higher in men and it is characterized by a relative dominance of SNS activity despite longer RR intervals compared to women [22]. In contrast, it has been shown, that respiratory events of men are longer, more frequent, and are accompanied by deeper oxygen desaturations compared to respiratory events of women [142, 143]. The results of this study could partially be explained by more severe intermittent oxygen desaturations of men: they may be at higher risk for more severe cyclical heart rate variation leading to increased variation of RR intervals. It is implied by the results of this thesis and previous literature that men and women should be studied separately when investigating HRV in OSA.

The use of only time-domain HRV parameters can be considered as the main limitation of this thesis. It is acknowledged that without frequency-domain HRV parameters it is impossible to precisely evaluate the spectral HRV variations or activities of SNS and PNS. However, an overview of the HRV can be obtained. The use of frequency-domain parameters would have been problematic as they often require a longer analysis period [3]. Furthermore, normative results for ultra-short-term HRV does not exist yet since short- and long-term measurements are considered to be the most appropriate options for assessing HRV [3, 5]. Nevertheless, promising results have been obtained showing that e.g. RMSSD could potentially be used for clinical ultra-short-term HRV analysis [3, 4]. More importantly, the ultra-short-term HRV analysis enables HRV analysis during and immediately after individual respiratory events, which would not be possible with HRV analyses based on a longer time window.

The use of automated R peak detection instead of manual analysis can be considered as another limitation of this study. Although the Pan-Tompkins method uses dual thresholding when detecting

the R peaks, it does not recognize e.g. irregular heart rhythms such as bi- or trigeminy [116]. However, with automated R peak detection, a large amount of data can be analyzed effectively, and the analysis is more easily reproducible. It is also acknowledged that disregarding arousals related to respiratory events or the sleep stage effects on HRV is a limitation. However, the focus of this study was to investigate the differences between respiratory event types, durations, and differences between sexes. Therefore, the effect of sleep stages or arousals were not considered as it would have made the focus too broad. RR intervals are shown to shorten in the adjacency of arousal in both OSA patients [144] and healthy subjects [128]: this thesis shows similar results (Figures 1-4). Moreover, previous studies have shown that in NREM, the PNS activity and short-term HRV increase, whereas in REM, SNS activity increases and HRV decreases [128, 129]. It has been also reported that HRV is modulated by sleep stages, perhaps even more strongly than OSA [59]: HRV is observed to gradually increase from N1 to N3 in NREM [127]. Therefore, further research studying inter-patient variation and the effects of arousals, sleep stages, and desaturations on ultra-short-term HRV are required.

In conclusion, this Master thesis provides valuable information about cardiovascular stress related to respiratory events in OSA since the changes in ultra-short-term HRV and RR interval variation reflect the immediate physiological consequences of apneas and hypopneas. A greater decrease in RR interval after the respiratory events and elevated ultra-short-term HRV are more strongly associated with longer duration of respiratory events, apneas, and male sex. The HR and HRV are modulated by the respiratory event duration and type. Therefore, a more detailed analysis of the respiratory event and cardiac characteristics could be a valuable complement to OSA diagnostics besides AHI.

References

1. Benjafield A V, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, Nunez CM, Patel SR, Penzel T, Pépin JLD, Peppard PE, Sinha S, Tufik S, Valentine K, Malhotra A. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir. Med.* 2019; 7: 687–698.

2. Berry RB, Brooks R, Gamaldo CE, Harding SM, Lloyd RM, Quan SF, Troester MM, Vaughn B V. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. *Am. Acad. Sleep Med.* 2017; 1–89.

3. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. *Front. Public Heal.* 2017; 5: 258.

4. Baek HJ, Cho CH, Cho J, Woo JM. Reliability of ultra-short-term analysis as a surrogate of standard 5-min analysis of heart rate variability. *Telemed. e-Health* 2015; 21: 404–414.

5. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996; 93: 1043–1065.

6. Goldberger JJ. Sympathovagal balance: How should we measure it? *Am. J. Physiol. - Hear. Circ. Physiol.* 1999; 276: 1273–1280.

7. Shaffer F, McCraty R, Zerr CL. A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. *Front. Psychol.* 2014; 5: 1040.

8. Zoccoli G, Amici R. Sleep and autonomic nervous system. *Curr. Opin. Physiol.* 2020; 15: 128–133.

9. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J. Clin. Invest.* 1995; 96: 1897–1904.

10. Punjabi NM. The Epidemiology of Adult Obstructive Sleep Apnea. *Proc. Am. Thorac. Soc.* 2008; 5: 136–143.

11. May AM, Van Wagoner DR, Mehra R. OSA and Cardiac Arrhythmogenesis: Mechanistic Insights. *Chest* 2017; 151: 225–241.

12. Di Fusco SA, Pignalberi C, Santini L, Colivicchi F, Santini M. Arrhythmias and sleep apnea: physiopathologic link and clinical implications. *J. Interv. Card. Electrophysiol.* 2020; 57: 387–397.

13. Arzt M, Young T, Finn L, Skatrud JB, Bradley TD. Association of sleep-disordered breathing and the occurrence of stroke. *Am. J. Respir. Crit. Care Med.* 2005; 172: 1447–1451.

14. Javier Nieto F, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing sleep apnea, and hypertension in a large community-based study. *J. Am. Med. Assoc.* 2000; 283: 1829–1836.

15. Urbanik D, Gać P, Martynowicz H, Poręba M, Podgórski M, Negrusz-Kawecka M, Mazur G, Sobieszczańska M, Poręba R. Obstructive sleep apnea as a predictor of reduced heart rate variability. *Sleep Med.* 2019; 54: 8–15.

16. Sequeira VCC, Bandeira PM, Azevedo JCM. Heart rate variability in adults with obstructive sleep apnea: A systematic review. *Sleep Sci.* 2019; 12: 214–221.

17. Narkiewicz K, Montano N, Cogliati C, Van De Borne PJH, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. *Circulation* 1998; 98: 1071–1077.

18. Sola-Soler J, Giraldo BF, Fiz JA, Jane R. Relationship between heart rate excursion and apnea duration in patients with Obstructive Sleep Apnea. *Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.* 2017. p. 1539–1542.

19. Kulkas A, Duce B, Leppänen T, Hukins C, Töyräs J. Severity of desaturation events differs between hypopnea and obstructive apnea events and is modulated by their duration in obstructive sleep apnea. *Sleep Breath.* 2017; 21: 829–835.

20. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T. Sleep Apnea and Cardiovascular Disease: An American Heart Association/American College of Cardiology Foundation scientific statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on. *Circulation* 2008; 118: 1080–1111.

21. Dewan NA, Nieto FJ, Somers VK. Intermittent hypoxemia and OSA: Implications for comorbidities. *Chest* 2015; 147: 266–274.

22. Ramaekers D, Ector H, Aubert AE, Rubens A, Van De Werf F. Heart rate variability and heart rate in healthy volunteers: Is the female autonomic nervous system cardioprotective? *Eur. Heart J.* 1998; 19: 1334–1341.

23. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population-A review on the epidemiology of sleep apnea. *J. Thorac. Dis.* 2015; 7: 1311–1322.

24. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, Mooser V, Preisig M, Malhotra A, Waeber G, Vollenweider P, Tafti M, Haba-Rubio J. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir. Med.* 2015; 3: 310–318.

25. AASM. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999; 22: 667–689.

26. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Am. Acad. Sleep Med. 2007.

27. Jordan AS, Mcsharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet* 2014; 383: 736–747.

28. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of Sleep Apnea. *Physiol. Rev.* 2010; 90: 47–112.

29. Eckert DJ, Malhotra A. Pathophysiology of Adult Obstructive Sleep Apnea. *Proc. Am. Thorac. Soc.* 2008; 5: 144–153.

30. Frost & Sullivan. Hidden Health Crisis Costing America Billions: Underdiagnosing and Undertreating Obstructive Sleep Apnea Draining Healthcare System. Am. Acad. Sleep Med. 2016.

31. Punjabi NM. COUNTERPOINT: Is the Apnea-Hypopnea Index the Best Way to Quantify the Severity of Sleep-Disordered Breathing? No. *Chest* 2016; 149: 16–19.

32. Pevernagie DA, Gnidovec-Strazisar B, Grote L, Heinzer R, McNicholas WT, Penzel T, Randerath W, Schiza S, Verbraecken J, Arnardottir ES. On the rise and fall of the apnea−hypopnea index: A historical review and critical appraisal. *J. Sleep Res.* 2020; 00: e13066.

33. Duce B, Milosavljevic J, Hukins C. The 2012 AASM Respiratory Event Criteria Increase the Incidence of Hypopneas in an Adult Sleep Center Population. *J. Clin. Sleep Med.* 2015; 11: 1425–1431.

34. Uniapnea [Internet]. Hengitysliitto [cited 2020 Jun 8].Available from: https://www.hengitysliitto.fi/fi/hengityssairaudet/uniapnea.

35. Senaratna C V., Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, Hamilton GS, Dharmage SC. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Med. Rev.* 2017; 34: 70–81.

36. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased Prevalence of Sleep-Disordered Breathing in Adults. *Am. J. Epidemiol.* 2013; 177: 1006–1014.

37. Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. *Am. J. Respir. Crit. Care Med.* 2003; 167: 1181–1185.

38. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. *J. Am. Med. Assoc.* 2000; 284: 3015–3021.

39. Young T, Peppard PE, Taheri S. Excess weight and sleep-disordered breathing. *J. Appl. Physiol.* 2005; 99: 1592–1599.

40. World Health Organization. Global surveillance, prevention and control of chronic respiratory diseases - a comprehensive approach. 2007.

41. Peromaa-Haavisto P, Tuomilehto H, Kössi J, Virtanen J, Luostarinen M, Pihlajamäki J, Käkelä P, Victorzon M. Prevalence of Obstructive Sleep Apnoea Among Patients Admitted for Bariatric Surgery. A Prospective Multicentre Trial. *Obes. Surg.* 2016; 26: 1384–1390.

42. Hillman D, Mitchell S, Streatfeild J, Burns C, Bruck D, Pezzullo L. The economic cost of inadequate sleep. *Sleep* 2018; 41: 1–13.

43. Mezzanotte WS, Tangel DJ, White DP. Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism). *J. Clin. Invest.* 1992; 89: 1571–1579.

44. Jordan AS, White DP, Lo YL, Wellman A, Eckert DJ, Yim-Yeh S, Eikermann M, Smith SA, Stevenson KE, Malhotra A. Airway dilator muscle activity and lung volume during stable breathing in obstructive sleep apnea. *Sleep* 2009; 32: 361–368.

45. Schwab RJ, Gupta KB, Gefter WB, Metzger LJ, Hoffman EA, Pack AI. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing: Significance of the lateral pharyngeal walls. *Am. J. Respir. Crit. Care Med.* 1995; 152: 1673–1689.

46. Burger CD, Stanson AW, Sheedy PF, Daniels BK, Shepard JW. Fast-computed tomography evaluation of age-related changes in upper airway structure and function in normal men. *Am. Rev. Respir. Dis.* 1992; 145: 846–852.

47. Berry RB, Gleeson K. Respiratory arousal from sleep: Mechanisms and significance. *Sleep* 1997; 20: 654–675.

48. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: A population health perspective. *Am. J. Respir. Crit. Care Med.* 2002; 165: 1217–1239.

49. Carrera M, Barbé F, Sauleda J, Tomás M, Gómez C, Santos C, Agustí AGN. Effects of obesity upon genioglossus structure and function in obstructive sleep apnoea. *Eur. Respir. J.* 2004; 23: 425–429.

50. Horner RL, Mohiaddin RH, Lowell DG, Shea SA, Burman ED, Longmore DB, Guz A. Sites and sizes of fat deposits around the pharynx in obese patients with obstructive sleep apnoea and weight matched controls. *Eur. Respir. J.* 1989; 2: 613–622.

51. Uniapnea (obstruktiivinen uniapnea aikuisilla). Käypä hoito -suositus. [Internet]. Suom. Lääkäris. Duodecim 2017 [cited 2020 Jun 10].Available from: https://www.kaypahoito.fi/hoi50088.

52. Al Lawati NM, Patel SR, Ayas NT. Epidemiology, Risk Factors, and Consequences of Obstructive Sleep Apnea and Short Sleep Duration. *Prog. Cardiovasc. Dis.* 2009; 51: 285–293.

53. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, Kales A. Prevalence of sleep-disordered breathing in women: Effects of gender. *Am. J. Respir. Crit. Care Med.* 2001; 163: 608–613.

54. Eikermann M, Jordan AS, Chamberlin NL, Gautam S, Wellman A, Lo YL, White DP, Malhotra A. The influence of aging on pharyngeal collapsibility during sleep. *Chest* 2007; 131: 1702–1709.

55. Wetter DW, Young TB, Bidwell TR, Badr MS, Palta M. Smoking as a Risk Factor for Sleep-Disordered Breathing. *Arch. Intern. Med.* 1994; 154: 2219–2224.

56. Young T, Peppard PE, Gottlieb DJ. Epidemiology of Obstructive Sleep Apnea. *Am. J. Respir. Crit. Care Med.* 2002; 165: 1217–1239.

57. Brain Basics: Understanding Sleep [Internet]. Natl. Inst. Neurol. Disord. Stroke 2019 [cited 2020 Jun 10].Available from: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Understanding-Sleep.

58. Findley LJ, Wilhoit SC, Suratt RM. Apnea duration and hypoxemia during REM sleep in patients with obstructive sleep apnea. *Chest* 1985; 87: 432–436.

59. Penzel T, Kantelhardt JW, Lo CC, Voigt K, Vogelmeier C. Dynamics of heart rate and sleep stages in normals and patients with sleep apnea. *Neuropsychopharmacology* 2003; 28: S48–S53.

60. Nikkonen S, Töyräs J, Mervaala E, Myllymaa S, Terrill P, Leppänen T. Intra-night variation in apnea-hypopnea index affects diagnostics and prognostics of obstructive sleep apnea. *Sleep Breath.* 2020; 24: 379–386.

61. Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: Anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. *Chest* 1997; 112: 629–639.

62. Seppä J, Tuomilehto H, Kokkarinen J. Aikuisten obstruktiivisen uniapnean hoito. *Duodecim.* 2007; 123: 88–94.

63. Sun Y, Ning Y, Huang L, Lei F, Li Z, Zhou G, Tang X. Polysomnographic characteristics of daytime sleepiness in obstructive sleep apnea syndrome. *Sleep Breath.* 2012; 16: 375–381.

64. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The Occurrence of Sleep-Disordered Breathing among Middle-Aged Adults. *N. Engl. J. Med.* 1993; 328: 1230–1235.

65. Foldvary-Schaefer NR, Waters TE. Sleep-Disordered Breathing. *Contin. (Minneap Minn)* 2017; 23: 1093–1116.

66. Chervin RD. Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea. *Chest* 2000; 118: 372–379.

67. Saunamäki T, Kilpinen R, Schwenson M, Tulppo J, Himanen S-L. Uniapnean kognitiiviset vaikutukset ja työkyky. *Duodecim* 2017; 133: 1999–2005.

68. Engleman HM, Douglas NJ. Sleep · 4: Sleepiness, cognitive function, and quality of life in obstructive apnoea/hypopnoea syndrome. *Thorax* 2004; 59: 618–622.

69. Saunamäki T, Jehkonen M. Depression and anxiety in obstructive sleep apnea syndrome: A review. Acta Neurol. Scand. 2007. p. 277–288.

70. Neau JP, Paquereau J, Bailbe M, Meurice JC, Ingrand P, Gil R. Relationship between sleep apnoea syndrome, snoring and headaches. *Cephalalgia* 2002; 22: 333–339.

71. Provini F, Vetrugno R, Lugaresi E, Montagna P. Sleep-related breathing disorders and headache. *Neurol. Sci.* 2006; 27: 149–152.

72. Russell MB. Sleep apnea headache: A growing concern in an increasingly obese population? *Expert Rev. Neurother.* 2013; 13: 1129–1133.

73. Alberti A, Mazzotta G, Gallinella E, Sarchielli P. Headache characteristics in obstructive sleep apnea syndrome and insomnia. *Acta Neurol. Scand.* 2005; 111: 309–316.

74. Zanation AM, Senior BA. The relationship between extraesophageal reflux (EER) and obstructive sleep apnea (OSA). *Sleep Med. Rev.* 2005; 9: 453–458.

75. Lavie P. Insomnia and sleep-disordered breathing. *Sleep Med.* 2007; 8.

76. Guilleminault C, Stoohs R, Duncan S. Snoring (I): Daytime sleepiness in regular heavy snorers. *Chest* 1991; 99: 40–48.

77. Myers KA, Mrkobrada M, Simel DL. Does this patient have obstructive sleep apnea? The rational clinical examination systematic review. *J. Am. Med. Assoc.* 2013; 310: 731–741.

78. Keropian B, Murphy N. The prevalence of OSA in snorers presenting with various chief complaints: A pilot study. *Cranio* 2014; 32: 217–218.

79. Arnardottir ES, Janson C, Bjornsdottir E, Benediktsdottir B, Juliusson S, Kuna ST, Pack AI, Gislason T. Nocturnal sweating - A common symptom of obstructive sleep apnoea: The Icelandic sleep apnoea cohort. *BMJ Open* 2013; 3.

80. Boron WF, Boulpaep EL. Medical physiology. Third edition. Elsevier; 2016.

81. Oksenberg A, Froom P, Melamed S. Dry mouth upon awakening in obstructive sleep apnea. *J. Sleep Res.* 2006; 15: 317–320.

82. Smith S, Sullivan K, Hopkins W, Douglas J. Frequency of insomnia report in patients with obstructive sleep apnoea hypopnea syndrome (OSAHS). *Sleep Med.* 2004; 5: 449–456.

83. Malhotra A, White DP. Obstructive sleep apnoea. *Lancet* 2002; 360: 237–245.

84. Kulkas A, Muraja-Murro A, Tiihonen P, Mervaala E, Töyräs J. Morbidity and mortality risk ratios are elevated in severe supine dominant OSA: a long-term follow-up study. *Sleep Breath.* 2014; 19: 653–660.

85. Young T, Finn L, Peppard P, Szklo-Coxe, Mariana Austin D, Nieto FJ, Stubbs R, Hla KM. Sleep Disordered Breathing and Mortality: Eighteen-Year Follow-up of the Wisconsin Sleep Cohort. *Sleep* 2008; 31: 1071–1078.

86. Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, Rapoport DM, Redline S, Resnick HE, Robbins JA, Shahar E, Unruh ML, Samet JM. Sleep-disordered breathing and mortality: A prospective cohort study. *PLoS Med.* 2009; 6.

87. Bassiri A, Guilleminault C. Clinical Features and Evaluation of Obstructive Sleep Apnea-Hypopnea Syndrome and Upper Airway Resistance Syndrome. *Princ. Pract. Sleep Med.* 4th ed. 2005. p. 1043–1052.

88. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Nieto FJ, O'Connor GT, Boland LL, Schwartz JE, Samet JM. Sleep-disordered Breathing and Cardiovascular Disease. *Am. J. Respir. Crit. Care Med.* 2001; 163: 19–25.

89. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Leiby BE, Vela-Bueno A, Kales A. Association of hypertension and sleep-disordered breathing. *Arch. Intern. Med.* 2000; 160: 2289–2295.

90. Young T, Peppard P, Palta M, Hla KM, Finn L, Morgan B, Skatrud J. Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Arch. Intern. Med.* 1997; 157: 1746–1752.

91. Maan A, Mansour M, Anter E, Patel V V., Cheng A, Refaat MM, Ruskin JN, Heist EK. Obstructive sleep apnea and Atrial fibrillation: Pathophysiology and implications for treatment. *Crit. Pathw. Cardiol.* 2015; 14: 81–85.

92. Monahan K, Storfer-Isser A, Mehra R, Shahar E, Mittleman M, Rottman J, Punjabi N, Sanders M, Quan SF, Resnick H, Redline S. Triggering of Nocturnal Arrhythmias by Sleep-Disordered Breathing Events. *J. Am. Coll. Cardiol.* 2009; 54: 1797–1804.

93. Peker Y, Carlson J, Hedner J. Increased incidence of coronary artery disease in sleep apnoea: A long-term follow-up. *Eur. Respir. J.* 2006; 28: 596–602.

94. Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE, Malouf JF, Ammash NM, Friedman PA, Somers VK. Association of atrial fibrillation and obstructive sleep apnea. *Circulation* 2004; 110: 364–367.

95. Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawabit R, Kirchner HL, Sahadevan J, Redline S. Association of nocturnal arrhythmias with sleep-disordered breathing: The sleep heart health study. *Am. J. Respir. Crit. Care Med.* 2006; 173: 910–916.

96. Elwood P, Hack M, Pickering J, Hughes J, Gallacher J. Sleep disturbance, stroke, and heart disease events: Evidence from the Caerphilly cohort. *J. Epidemiol. Community Health* 2006; 60: 69–73.

97. Nakamura S, Asai K, Kubota Y, Murai K, Takano H, Tsukada YT, Shimizu W. Impact of sleep-disordered breathing and efficacy of positive airway pressure on mortality in patients with chronic heart failure and sleep-disordered breathing: a meta-analysis. *Clin. Res. Cardiol.* 2015; 104: 208–216.

98. Collop NA, Anderson WMD, Boehlecke B, Claman D, Goldberg R, Gottlieb DJ, Hudgel D, Sateia M, Schwab R. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. *J. Clin. Sleep Med.* 2007; 3: 737–747.

99. Sovijärvi A, Länsimies E, Savolainen S, Turjanmaa V, Vanninen E. Unenaikaisten hengityshäiriöiden tutki-minen. *Kliin. Fysiol. ja Isotooppilääket.* Helsinki: Duodecim; 2003.

100. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, Harrod CG. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: An American academy of sleep medicine clinical practice guideline. *J. Clin. Sleep Med.* 2017; 13: 479–504.

101. Muraja-Murro A, Nurkkala J, Tiihonen P, Hukkanen T, Tuomilehto H, Kokkarinen J, Mervaala E, Töyräs J. Total duration of apnea and hypopnea events and average desaturation show significant variation in patients with a similar apnea-hypopnea index. *J. Med. Eng. Technol.* 2012; 36: 393–398.

102. Leppänen T. Novel methods for diagnostics of obstructive sleep apnea: effect of weight loss, gender, and sleeping position on severity of apnea, hypopnea and desaturation events. Doctoral thesis, University of Eastern Finland; 2016.

103. Kinnula V, Tukiainen P, Laitinen LA. Keuhkosairaudet. 1st ed. Duodecim Kustannus Oy; 1997.

104. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, Mediano O, Chen R, Drager LF, Liu Z, Chen G, Du B, McArdle N, Mukherjee S, Tripathi M, Billot L, Li Q, Lorenzi-Filho G, Barbe F, Redline S, Wang J, Arima H, Neal B, White DP, Grunstein RR, Zhong N, Anderson CS. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. *N. Engl. J. Med.* 2016; 375: 919–931.

105. Mineiro MA, Silva PM da, Alves M, Papoila AL, Marques Gomes MJ, Cardoso J. The role of sleepiness on arterial stiffness improvement after CPAP therapy in males with obstructive sleep apnea: a prospective cohort study. *BMC Pulm. Med.* 2017; 17: 182.

106. Wimms AJ, Kelly JL, Turnbull CD, McMillan A, Craig SE, O'Reilly JF, Nickol AH, Hedley EL, Decker MD, Willes LA, Calverley PMA, Benjafield A V, Stradling JR, Morrell MJ, West SD, Simonds AK, Withana S, Pepperell JC, Ward NR, Kent BD, Quinnell T, Paracha M, Anderson W. Continuous positive airway pressure versus standard care for the treatment of people with mild obstructive sleep apnoea (MERGE): a multicentre, randomised controlled trial. *Lancet Respir. Med.* 2020; 8: 349–358.

107. Freedman N. Treatment of Obstructive Sleep Apnea: Choosing the Best Positive Airway Pressure Device. *Sleep Med. Clin.* 2017; 12: 529–542.

108. Kulkas A, Leppänen T, Sahlman J, Tiihonen P, Mervaala E, Kokkarinen J, Randell J, Seppä J, Töyräs J, Tuomilehto H. Amount of weight loss or gain influences the severity of respiratory events in sleep apnea. *Med. Biol. Eng. Comput.* 2015; 53: 975–988.

109. Tuomilehto H, Seppä J, Uusitupa M. Obesity and obstructive sleep apnea - Clinical significance of weight loss. *Sleep Med. Rev.* 2013; 17: 321–329.

110. Won CHJ, Li KK, Guilleminault C. Surgical treatment of obstructive sleep apnea: Upper airway and maxillomandibular surgery. *Proc. Am. Thorac. Soc.* 2008; 5: 193–199.

111. Pumprla J, Howorka K, Groves D, Chester M, Nolan J. Functional assessment of heart rate variability: Physiological basis and practical applications. *Int. J. Cardiol.* 2002; 84: 1–14.

112. Abdelnabi M. Cardiovascular clinical implications of heart rate variability. *Int. J. Cardiovasc. Acad.* 2019; 5: 37.

113. Nunan D, Sandercock GRH, Brodie DA. A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. *PACE - Pacing Clin. Electrophysiol.* 2010; 33: 1407–1417.

114. Leppäluoto J, Rintamäki H, Vakkuri O, Vierimaa H, Lauri T. Anatomia + fysiologia: rakenteesta toimintaan. 9th ed. Sanoma Pro Oy; 2019.

115. Opthof T. The normal range and determinants of the intrinsic heart rate in man. *Cardiovasc. Res.* 2000; 45: 177–184.

116. Pan J, Tompkins WJ. A Real-Time QRS Detection Algorithm. *IEEE Trans. Biomed. Eng.* 1985; 32: 230–236.

117. Xhyheri B, Manfrini O, Mazzolini M, Pizzi C, Bugiardini R. Heart Rate Variability Today. *Prog. Cardiovasc. Dis.* 2012; 55: 321–331.

118. Kleiger RE, Stein PK, Bigger JT. Heart rate variability: Measurement and clinical utility. *Ann. Noninvasive Electrocardiol.* 2005; 10: 88–101.

119. Carney RM, Blumenthal JA, Stein PK, Watkins L, Catellier D, Berkman LF, Czajkowski SM, O'Connor C, Stone PH, Freedland KE. Depression, heart rate variability, and acute myocardial infarction. *Circulation* 2001; 104: 2024–2028.

120. Umetani K, Singer DH, McCraty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: Relations to age and gender over nine decades. *J. Am. Coll. Cardiol.* 1998; 31: 593–601.

121. Antelmi I, De Paula RS, Shinzato AR, Peres CA, Mansur AJ, Grupi CJ. Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. *Am. J. Cardiol.* 2004; 93: 381–385.

122. Jäncke L, Mérillat S, Liem F, Hänggi J. Brain size, sex, and the aging brain. *Hum. Brain Mapp.* 2015; 36: 150–169.

123. Liao D, Barnes RW, Chambless LE, Simpson RJ, Sorlie P, Heiss G, The ARIC Investigators. Age, race, and sex differences in autonomic cardiac function measured by spectral analysis of heart rate variability-The ARIC study. *Am. J. Cardiol.* 1995; 76: 906–912.

124. Huikuri H V., Pikkujämsä SM, Airaksinen KEJ, Ikäheimo MJ, Rantala AO, Kauma H, Lilja M, Kesäniemi YA. Sex-Related Differences in Autonomic Modulation of Heart Rate in Middle-aged Subjects. *Circulation* 1996; 94: 122–125.

125. Liu CC, Kuo TBJ, Yang CCH. Effects of estrogen on gender-related autonomic differences in humans. *Am. J. Physiol. - Hear. Circ. Physiol.* 2003; 285: 2188–2193.

126. Stein PK, Pu Y. Heart rate variability, sleep and sleep disorders. *Sleep Med. Rev.* 2012; 16: 47–66.

127. Tobaldini E, Nobili L, Strada S, Casali KR, Braghiroli A, Montano N. Heart rate variability in normal and pathological sleep. *Front. Physiol.* 2013; 4: 1–11.

128. Bonnet MH, Arand DL. Heart rate variability: Sleep stage, time of night, and arousal influences. *Electroencephalogr. Clin. Neurophysiol.* 1997; 102: 390–396.

129. Gammoudi N, Cheikh R Ben, Saafi MA, Sakly G, Dogui M. Cardiac autonomic control in the obstructive sleep apnea. *Libyan J. Med.* 2015; 10: 26989.

130. Guilleminault C, Winkle R, Connolly S, Melvin K, Tilkian A. Cyclical variation of the heart rate in sleep apnea syndrome. Mechanisms, and Usefulness of 24 h Electrocardiography as a Screening Technique. *Lancet* 1984; 323: 126–131.

131. Joyner MJ, Limberg JK, Wehrwein EA, Johnson BD. Role of the carotid body chemoreceptors in glucose homeostasis and thermoregulation in humans. *J. Physiol.* 2018; 596: 3079–3085.

132. Gilat H, Vinker S, Buda I, Soudry E, Shani M, Bachar G. Obstructive sleep apnea and cardiovascular comorbidities: A large epidemiologic study. *Med.* 2014; 93: e45.

133. Tarvainen MP, Ranta-aho PO, Karjalainen PA. An advanced detrending method with application to HRV analysis. *IEEE Trans. Biomed. Eng.* 2002; 49: 172–175.

134. Zwillich C, Devlin T, White D, Douglas N, Weil J, Martin R. Bradycardia during sleep apnea. Characteristics and mechanism. *J. Clin. Invest.* 1982; 69: 1286–1292.

135. Chouchou F, Pichot V, Barthélémy JC, Bastuji H, Roche F. Cardiac sympathetic modulation in response to apneas/hypopneas through heart rate variability analysis. *PLoS One* 2014; 9: 1–10.

136. Leppänen T, Kulkas A, Oksenberg A, Duce B, Mervaala E, Töyräs J. Differences in arousal probability and duration after apnea and hypopnea events in adult obstructive sleep apnea patients. *Physiol. Meas.* 2018; 39.

137. Alex R, Manchikatla S, Machiraju K, Altuwaijri E, Watenpaugh E, Zhang R, Behbehani K. Effect of apnea duration on apnea induced variations in cerebral blood flow velocity and arterial blood pressure. *36th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.* 2014. p. 270–273.

138. Wu H, Zhan X, Zhao M, Wei Y. Mean apnea – hypopnea duration (but not apnea – hypopnea index) is associated with worse hypertension in patients with obstructive sleep apnea. *Med.* 2016; 95: e5493.

139. Butler MP, Emch JT, Rueschman M, Sands SA, Shea SA, Wellman A, Redline S. Apnea-hypopnea event duration predicts mortality in men and women in the sleep heart health study. *Am. J. Respir. Crit. Care Med.* 2019; 199: 903–912.

140. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. *N. Engl. J. Med.* 2005; 352: 1206–1214.

141. Dekker JM, Schouten EG, Klootwijk P, Pool J, Swenne CA, Kromhout D. Heart Rate Variability from Short Electrocardiographic Recordings Predicts Mortality from All Causes in Middle-aged and Elderly Men: The Zutphen Study. *Am. J. Epidemiol.* 1997; 145: 899–908.

142. Ware JC, McBrayer RH, Scott JA. Influence of Sex and Age on Duration and Frequency of Sleep Apnea Events. *Sleep* 2000; 23: 165–170.

143. Leppänen T, Kulkas A, Duce B, Mervaala E, Töyräs J. Severity of individual obstruction events is gender dependent in sleep apnea. *Sleep Breath.* 2017; 21: 397–404.

144. Smith JH, Baumert M, Nalivaiko E, McEvoy RD, Catcheside PG. Arousal in obstructive sleep apnoea patients is associated with ECG RR and QT interval shortening and PR interval lengthening. *J. Sleep Res.* 2009; 18: 188–195.