Assessment of Peripheral Arterial Tone

– Clinical Applications in Sleep Medicine

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This thesis is dedicated to

my parents, my sister Hong,

Liying and Wenxi

ABSTRACT

Circulatory and vascular control differs between wakefulness and sleep. Few studies have used physiological recordings during sleep for assessment of cardiovascular (CV) function and risk. This thesis addresses the physiological link between nocturnal peripheral vascular tone, measured by a novel finger photoplethysmographic signal – PAT (peripheral arterial tone), and obstructive sleep apnea (OSA). The validity of using such a signal for OSA diagnostics and CV risk classification is also studied.

The amplitude of the PAT signal was periodically attenuated, reflecting vasoconstriction, during the immediate post apnea/hypopnea period. These attenuations were largely reversed by cumulative dosages of phentolamine (α-receptor antagonist) infusion via the brachial artery during sleep in eight patients with severe OSA. This effect suggests that OSA-related PAT attenuation is mediated via a sympathoadrenergic α-receptor mechanism.

Adrenergic α-receptor mechanisms were further evaluated in a double-blind crossover study comparing equipotent dosages of doxazosin (a peripheral α-receptor inhibitor) and enalapril (an angiotensin-converting enzyme inhibitor) on digital vasoconstriction and nocturnal blood pressure (BP). While the nighttime beat-to-beat finger BP was significantly higher under doxazosin treatment, the apnea related PAT attenuation decreased during doxazosin compared with enalapril treatment ($P<0.001$) in 16 hypertensive OSA patients. An analysis of sleep related changes of PAT demonstrated that attenuations were influenced by apnea related oxygen desaturation and rapid eye movement sleep.

A portable monitoring device, Watch_PAT100 (WP100), was validated against unattended polysomnography (PSG) for OSA diagnosis in 98 subjects recruited from the Skaraborg Hypertension and Diabetes Project. The WP100 records PAT, pulse rate, oxygen saturation and actigraphy for automatic analysis of the sleep-wake state, respiratory disturbance index (RDI), apnea-hypopnea index (AHI) and oxygen desaturation index (ODI). The WP100 RDI, AHI, and ODI correlated closely with the corresponding indices obtained by PSG. The area under the ROC curves for WP100 AHI and RDI were 0.93 and 0.90 when the AHI and RDI thresholds 10 and 20 were applied, respectively. A new standard for limited-channel device validation using simultaneous PSG recording in the home environment was proposed.

The relationship between nocturnal PAT attenuation and office BP was investigated in 81 subjects from the same study population. Episodic attenuations of the PAT signal were identified and characterized. In a generalized least squares regression model, we found an association between median PAT attenuation (PWA.att) and office BP which was independent of gender, age, body mass index, antihypertensive medication, number of attenuation episodes, AHI, ODI and arousal index. Each 10% increase in PWA.att was associated with an increase of 5.0 mmHg systolic BP and 3.0 mmHg diastolic BP, respectively. Continuous assessment of PAT during sleep appears to reflect vascular regulation and homeostasis.

An autonomic state indicator algorithm based on a novel finger pulse oximetry sensor was developed and validated for CV risk assessment according to the ESH/ESC risk factor matrix. Five signal components reflecting cardiac and vascular activity (pulse wave attenuation, pulse rate acceleration, pulse propagation time, respiration related pulse oscillation and oxygen desaturation) were extracted in 99 subjects and used to construct an algorithm. The capacity of the algorithm for CV risk prediction was validated in 49 additional subjects. The sensitivity and specificity of the algorithm to distinguish high/low CV risk in the validation group was 80% and 77%, respectively. The area under the ROC curve for high CV risk classification was 0.84. Based on this data, we propose that information derived from a photoplethysmographic signal obtained during sleep may be applied as a useful tool for CV risk classification.

This thesis supports the notion that PAT, as a measure of finger pulsatile volume changes, reflects the sympathetic autonomic activity and can be used for the detection of sleep disordered breathing. Information derived from an oximeter based pulse wave signal may be used to assess CV function and CV risk.

Keywords: Arousal, autonomic nervous system, blood pressure, cardiovascular risk, obstructive sleep apnea, peripheral arterial tone, portable monitoring, pulse wave attenuation

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LIST OF PAPERS

This thesis is based on the following studies, which will be referred to in the text by Roman numerals.

I. Zou D, Grote L, Eder DN, Peker Y, Hedner J.
Obstructive apneic events induce alpha-receptor mediated digital vasoconstriction.
Sleep 2004; 27(3): 485-9.

II. Zou D, Grote L, Eder DN, Radlinski J, Hedner J.
A double-blind crossover study of doxazosin and enalapril on peripheral vascular tone and nocturnal blood pressure in sleep apnea patients.
Sleep Medicine 2010; 11(3): 325-28

III. Zou D, Grote L, Peker Y, Lindblad U, Hedner J.
Validation a portable monitoring device for sleep apnea diagnosis in a population based cohort using synchronized home polysomnography.
Sleep 2006; 29(3): 367-74.

IV. Zou D, Grote L, Radlinski J, Eder DN, Lindblad U, Hedner J.
Nocturnal pulse wave attenuation is associated with office blood pressure in a population based cohort.
Sleep Medicine 2009; 10(8): 836-43.

V. Grote L, Sommermeyer D, Zou D, Eder DN, Hedner J
Oximeter based autonomic state indicator algorithm for cardiovascular risk assessment.
Chest. In press.

ABBREVIATIONS

AASM	American academy of sleep medicine
AHI	Apnea hypopnea index
ARI	Arousal index
ASI	Autonomic state indicator
AUC	Area under curve
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CPAP	Continuous positive airway pressure
CSB	Cheyne-Stokes breathing
CV	Cardiovascular
DO	Doxazosin
EEG	Electroencephalogram
EMG	Electromyography
EN	Enalapril
EOG	Electrooculography
ESH/ESC	European Society of Hypertension/European Society of Cardiology
ESS	Epworth sleepiness scale
HDL	High density lipoprotein
HF	High frequency
HR	Heart rate
LF	Low frequency
MAP	Mean arterial pressure
MSNA	Muscle sympathetic nerve activity
NREM	Non-rapid eye movement
ODI	Oxygen desaturation index

OSA	Obstructive sleep apnea
PAT	Peripheral arterial tone
PM	Portable monitoring
PPT	Pulse propagation time
PR	Pulse rate
PR-I	Pulse rate acceleration index
PSG	Polysomnography
PTT	Pulse transit time
PWA	Pulse wave amplitude
PWA.att	Median PAT attenuation
PWA-I	Pulse wave attenuation index
RDI	Respiratory disturbance index
REM	Rapid eye movement
RERA	Respiratory effort-related arousal
R&K	Rechtschaffen and Kales
ROC	Receiver operating characteristic
RRPO	Respiration related pulse oscillation
SDB	Sleep disordered breathing
SpO_2–I	Hypoxia index
TNF	Tumor necrosis factor
WP100	Watch_PAT100

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INTRODUCTION

1.1 The physiology during normal sleep

The description of sleep and dreams can be traced back to the earliest civilizations, including China, India, Mesopotamia and Egypt. While ancient Greek and Roman philosophers often concerned themselves with the nature of dreaming,[1] the sleep/wake cycle was regarded as the shift of the "Yin/Yang" force in Chinese traditional medicine. More has been learned about sleep in the past century than during the preceding 5,000 years. With the use of electroencephalogram (EEG), Hans Berger recorded the wake and sleep rhythms in man for the first time in 1930.[2] Later, Loomis et al. showed that EEG patterns changed dramatically during sleep.[3] This was followed by the recognition of cyclical patterns of different sleep stages, including rapid eye movement (REM) sleep.[4] In 1968, a committee chaired by Rechtschaffen and Kales (R&K) recommended that sleep is classified based on EEG brain waves, eye movements from electrooculography (EOG) and mental/submental muscle tone from electromyography (EMG).[5] Sleep was divided into non-rapid eye movement (NREM) (including stages 1, 2, 3 and 4) and REM sleep. The R&K classification has been used as an international standard for sleep studies since then. Based on the R&K classification, the American Academy of Sleep Medicine (AASM) recently published the manual for the scoring of sleep and associated events (Table 1).[6]

1.1.1 Breathing during normal sleep

From a stability point of view, sleep includes unsteady NREM sleep (sleep stage 1 and short periods of stage 2 interrupted by arousal), steady NREM sleep (stable sleep stage 2, stage 3 and 4) and REM sleep. Respiratory function during sleep is not uniform, but rather state-dependent.

In brief, unsteady NREM sleep is associated with instability of breathing ranging from small fluctuations in breathing amplitude to periodic breathing. During consolidated NREM sleep, there is remarkably regular amplitude and frequency of breathing. Minute ventilation decreases about 13% in sleep stage 2 and 15% in stage 3 and 4 compared to wakefulness,[7] which is attributed mainly to a decrease in tidal volume. REM sleep is characterized by shallow breathing

Table 1. Comparisons of two current sleep stage scoring criteria (adapted from reference[5,6,8]).

	R&K sleep staging criteria	AASM sleep stage scoring criteria
Wakefulness	Stage Wake: >50% of the epoch consists of alpha (8-13 Hz) activity and/or low voltage, mixed frequency activity.	Stage W: >50% of the epoch consists of alpha activity. Eye blinks at a frequency of 0.5-2 Hz or reading eye movements. Irregular REM associated with normal or high chin muscle tone.
NREM sleep	Stage 1: 50% of the epoch consists of relatively low voltage, mixed frequency (2-7 Hz) EEG activity without REMs. Slow rolling eye movements lasting several seconds often seen in early stage 1.	Stage N1: 50% of the epoch consists of low amplitude, mixed frequency (4-7 Hz) activity, and/or vertex sharp waves, slow eye movements.
	Stage 2: Appearance of sleep spindles and/or K complexes on a background of relatively low voltage, mixed frequency EEG activity. <20% of the epoch may contain high voltage (>75μV, <2 Hz) activity.	Stage N2: Appearance of sleep spindles and/or K complexes on a background of relatively low voltage, mixed frequency EEG activity. <20% of the epoch may slow wave activity.
	Stage 3: Moderate amounts (20%-50%) of high amplitude, slow wave activity of the epoch.	Stage N3: 20% or more of an epoch consists of slow wave activity (frequency 0.5-2 Hz, peak-to-peak amplitude >75μV), irrespective of age.
	Stage 4: Large amounts (>50%) of the epoch consists of high amplitude, slow wave activity.	
REM sleep	Stage REM: Relatively low voltage mixed (2-7 Hz) frequency EEG with episodic REMs and low chin EMG activity.	Stage R: Low amplitude, mixed frequency EEG, low chin EMG tone and REMs.
Movement	Movement Time: The polygraph record is obscured by movements of the subject.	Major body movement: Movement and muscle artifact obscuring the EEG for more than half an epoch.

with irregularities linked to burst of eye movements. However, minute ventilation, tidal volume and respiratory rate seem to differ little from NREM sleep.[9]

1.1.2 Hemodynamic changes during sleep

Both animal and human studies have shown that heart rate (HR) and systemic blood pressure (BP) decrease from wakefulness to NREM sleep. REM sleep is

characterized by increased and large variations of HR and BP compared with NREM sleep, presumably reflecting the phasic REM events.

BP is modulated by cardiac output and peripheral resistance. Using intra-arterial catheters, Khatri and Freis found a significant decrease of cardiac output during NREM sleep compared to awakening, but no change of total peripheral resistance. Moreover, stroke volume did not change during NREM sleep suggesting that the reduction of cardiac output is likely a consequence of decreased HR rather than stroke volume change.[10]

1.1.3 Autonomic regulation during sleep

Autonomic regulations during sleep are complex, sleep stage dependent and regionally differentiated. Using HR spectral analysis as the overall measure of autonomic control, NREM sleep was found to be associated with reduced sympathetic component and an increased in parasympathetic outflow compared with wakefulness. REM sleep, in this aspect, is similar to wakefulness.[9] Peripheral vascular smooth muscle sympathetic nerve activity (MSNA), measured by microneurography, is also reduced by approximately 50% (stage 4) during NREM sleep and doubled during REM sleep compared with wakefulness.[11,12]

However, regional differences in sympathetic output during sleep may exist. For instance, sympathetic activity in vasoconstrictor fibers of limb skeletal muscle is increased in parallel with reduced output to the splanchnic, cardiac, lumbar and renal vascular beds in a pharmacological model of REM sleep.[13] As an indirect measure of vasomotor tone, recordings of regional blood flow changes during sleep also supports this notion. While cerebral blood flow[14,15] and left coronary blood flow[16] decreased in NREM sleep and increased in REM sleep, renal[17] and splanchnic[18] blood flow remained unchanged throughout the sleep/wake cycle. Muscle blood flow, on the other hand, showed no change in the transition from wakefulness to NREM sleep, but decreased during REM sleep.[9] Skin blood flow measured by laser Doppler showed a clear increase during sleep compared with wakefulness possibly due to thermolytic vasodilation, but no changes within different sleep stages.[19]

1.1.4 Sleep regulation

Several components including sleep homeostasis and circadian control contribute to sleep regulation. Sleep homeostasis, defined as the sleep-wake balance prior to a period of sleep and waking, serves as an important regulator

of the level of sleep. The circadian clock provides an endogenous rhythmicity which maintains periodic changes independent of prior sleep and waking. In the famous "two-process model"[20], sleep propensity is postulated to increase when homeostasis process (process S) rises during waking with the regulation of circadian process (process C), which increases sleep propensity at a specific time of the day. Using a forced desynchrony protocol, slow wave sleep (NREM stage 3 and 4) was found mainly influenced by the homeostatic whereas REM sleep was controlled by both homeostatic and circadian factors.[21]

1.2 Sleep disordered breathing

1.2.1 Historical perspective

Like many other diseases, the initial description of sleep disordered breathing (SDB) was through clinical observation. While Cheyne-Stokes breathing (CSB) was observed in the early to mid 19th century, a condition characterized by obesity and extreme excessive sleepiness was described in 1889[22] and referred to as the "Pickwickian syndrome" by Burwell et al. in 1956.[23] This was followed by the first physiological recordings in sleeping Pickwickian patients in the early 1960s,[24,25] linking the disease to cessation of breathing during sleep in 1965,[26] and attributing the apenic events to obstruction of the upper airway in 1966.[27] Convinced by the importance of the findings, Lugaresi and Coccagna organized the first "Sleep Disorders" conference in Bologna in 1967, an event which opened the preface of modern sleep medicine.[28]

1.2.2 Definitions of sleep related breathing disorder

Sleep related breathing disorders can be subdivided into central sleep apnea syndrome, obstructive sleep apnea syndrome and the sleep related hypoventilation/hypoxemic syndrome.[29] The definitions of different types of SDB during sleep are shown in Table 2. This thesis will focus on obstructive sleep apnea (OSA), the most common SDB in the general population.

1.2.3 Epidemiology of OSA

The term "obstructive sleep apnea" was first used by Guilleminault et al. in 1976.[30] The disorder gained much attention outside the sleep medicine field following the first major epidemiologic study published by Young et al. in 1993.[31] A group of 602 state employees aged 30–60 years (the Wisconsin Sleep

Table 2. Definitions of different sleep breathing disorders.[6]

Apnea	≥90% thermal sensor flow reduction compared to baseline, lasts at least 10 s	**Obstructive apnea**: continued/increased inspiratory effort during the apnea
		Central apnea: absent inspiratory effort during the apnea
		Mixed apnea: absent inspiratory effort in the initial portion of the apnea, followed by resumption of inspiratory effort in the second portion of the event
Hypopnea	**Criteria A**: ≥30% nasal flow reduction compared to baseline, ≥4% desaturation from baseline, lasts at least 10 s Or **Criteria B**: ≥50% nasal flow reduction compared to baseline, ≥3% desaturation from baseline or event associated with arousal, lasts at least 10 s	
Respiratory effort-related arousal (RERA)	Increasing respiratory effort or flattening of the nasal pressure leading to an arousal, at least 10 s, not fulfill the apnea/hypopnea criteria	
Cheyne-Stokes breathing	At least 3 consecutive cycles of cyclical crescendo and decrescendo change in breathing with at least one of the following: 1 central apnea/hypopnea ≥5 events/hr 2 at least 10 consecutive minutes	
Hypoventilation	≥10 mmHg increase in $PaCO_2$ during sleep compared to awake supine value	

Cohort) underwent an in-lab polysomnography (PSG) study. OSA defined as apnea hypopnea index (AHI) ≥5 was found in 9% women and 24% men, whereas 2% of women and 4% of men had OSA plus daytime sleepiness. Subsequent large population-based sleep studies[32-34] estimated that mild OSA (AHI ≥5) occurs in 20% of adults while 1 out of every 15 adults has moderate to severe OSA (AHI ≥15).[35]

OSA is a predominantly male disease.[36] The male/female ratio in a sleep clinic cohort can be as high as 8:1, whereas in population studies the ratio among the undiagnosed cases is about 2:1.[37] This discrepancy highlights the fact that OSA in women is under-diagnosed and under-treated. The reason for this difference is complex. Possible explanations are that female patients have different clinical

presentations (like snoring) than males or are more reluctant to report symptoms.

The prevalence of OSA also increases with age throughout midlife with a plateau after 65 years.[38] The prevalence of OSA in the elderly (≥65 years) is 2 to 3-fold higher than in the middle aged (30-64 years).[37] Although a complete understanding of the underlying mechanism is lacking, anatomy and neural reflex impairment seem to contribute to these changes. Another character in older group is that central sleep apneas are much more prevalent.[32] However, the impact of sleep apnea on clinical outcomes in the elderly group is still unclear.[39,40]

1.2.4 Risk factors for OSA

Several risk factors have been associated with an increased prevalence of OSA. Obesity is well established and occurs in approximately 70% of all OSA patients. A 10% increase in body weight was associated with a 6-fold great risk of developing moderate to severe OSA in a prospective 4-year follow-up study.[41] Obesity could cause pharyngeal airway narrowing and ventilatory control instability, thereby increase the propensity for OSA.

Craniofacial and upper airway abnormalities may also contribute to OSA. In 142 nonclinical male subjects, a narrow horizontal dimension of the maxilla was found to increase the probability of having moderate to severe OSA 5 to 7 fold in nonobese subjects and 3 fold in obese subjects.[42] The thickness of the lateral pharyngeal muscular walls was demonstrated as the predominant anatomic factor causing airway narrowing in OSA subjects.[43] Other anatomy risk factors for OSA include retroposed mandible/maxillae, adenotonsillar hypertrophy and macroglossia.

Alcohol ingestion can decrease pharyngeal airway size and increase nasal resistance.[44] Most epidemiologic studies have demonstrated that alcohol use before sleep increased number and duration of respiratory events during sleep.[35] Similarly, drugs that cause central nervous system depression (such as opioids and benzodiazepines) can also exacerbate OSA.

The association between OSA and smoking is not well studied although smokers were reported three times more likely to have OSA compared to nonsmoker or former smokers in the Wisconsin cohort.[45] Airway inflammation may be the potential mechanism for smoking as a risk factor for OSA.

Nighttime nasal obstruction could lead to mouth breathing during sleep predisposing to airway collapse and has been associated with the occurrence of snoring[46] and OSA[47]. Participants with chronic nighttime rhinitis in the well established Wisconsin sleep cohort were twice likely to report habitual snoring and 1.8 times more likely to have moderate to severe OSA (AHI>15) compared to those without nasal congestion.[48]

Female hormone status has a substantial impact on upper airway dilator muscle activity.[49] A postmenopausal state was associated with four fold higher prevalence of OSA compared with premenopausal women in a cross sectional study.[33] Post menopausal women on hormone replacement therapy had significantly lower OSA occurrence compared to non-treated subjects suggesting that hormone depletion is a risk factor for OSA in the female population.[33,50]

1.2.5 Genetics of OSA

OSA is likely to be a complex, polygenic disease involving many etiological factors including obesity, craniofacial structure, upper airway muscle and central ventilatory control. The two genome-wide scan studies[51,52] performed with a target on SDB identified certain candidate regions in this disorder. However, the statistically significant association was lost after adjustment for body mass index (BMI). Findings from candidate gene studies were not consistently replicated and hampered by underpowered, poorly controlled designs.[53] Studies on family aggregation cases with OSA have found an increase of OSA risk varying from 1.5 to 2.0 fold in first degree relatives.[54]

1.2.6 Pathogenesis of OSA

The human upper airway is flexible without rigid support due to the evolution of speech. Factors contributing pharyngeal airway collapse during sleep may contribute to the pathogenesis of OSA. A narrow pharyngeal airway naturally increases the vulnerability to OSA[55] and anatomical abnormalities such as excess soft tissue around the airway have been associated with OSA patients.[43,56]

Upper airway patency is maintained by pharyngeal dilator muscles activation (Figure 1) and sleep is associated with reduced tonic muscle activity, diminished neuromuscular reflexes and increased pharyngeal resistance. Therefore, the vulnerability for upper airway collapse is greater during sleep. Studies have shown that pharyngeal dilator muscle activation during

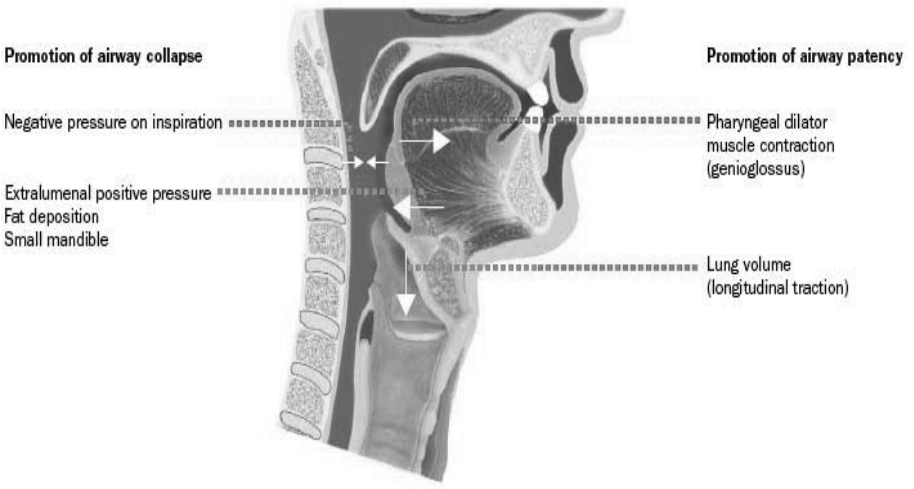

Figure 1. Driving force of the upper airway. Inspiratory negative pressure and extraluminal positive pressure tend to promote pharyngeal collapse. Upper airway dilator muscles and increased lung volume tend to maintain pharyngeal patency. (Reprinted from Malhotra A and White DP. Lancet 2002; 360: 237-45, with permission from Elsevier).[57]

wakefulness was higher in OSA patients compared with control subjects.[58] Hence, a sleep-related insufficient muscular response to negative pressure during inspiration may be an important mechanism in OSA.

Afferent neurogenic lesions that potentially influence upper airway reflex mechanisms may also contribute to the development of OSA.[59,60] It has been hypothesized that snoring vibrations can lead to impaired detection of mechanical stimuli in the pharyngeal airway and thereby may exacerbate OSA.[61] This notion is supported by data suggesting denervation changes of upper airway dilatory muscles in snoring and OSA patients.[62,63]

The arousal threshold to respiratory stimuli and the ventilatory control stability are also contributors to airway functional integrity during sleep. As an indicator of ventilatory control stability, loop gain was found to correlate with apnea severity in patients with a moderately collapsible airway.[64]

1.2.7 Acute hemodynamic and autonomic changes of OSA

OSA events are typically characterized by repetitive cessation of airflow accompanied by increased respiratory effort. Associated pathophysiological features include hypoxemia, hypercapnia, negative intrathoracic pressure, and arousal from sleep. As a consequence, hemodynamic and cardiovascular (CV) autonomic control oscillate along with the apneic and ventilatory phases. Hemodynamic effects of sleep apnea were first described by Coccagna and colleagues from Bologna at the "Hypersomnia and Periodic Breathing" conference held in 1972.[65] Several subsequent studies conducted by the Stanford group and others have further elucidated various acute physiological effects of apnea.[66-69]

The HR changes during the apnea-recovery cycle are complex and sometimes variable.[70] Bradycardia is commonly seen during apnea phase (diving reflex) followed by transient tachycardia with resumption of breathing (vagolytic effects of lung inflation and arousal). The HR subsequently resumes a normal level (baroreceptor activation) until next apnea begins. Other studies reported a HR rise during apnea and a further rise at apnea termination.[68,71] The severity of hypoxia as well as individual differences in hypoxic chemosensitivity may further influence the sympathetic/vagal output thereby causing variability of HR response during OSA.[72]

During apnea, there is a development of exaggerated negative intrathoracic pressure as a result of inspiratory attempts against the closed pharynx. As a result, cardiac left ventricular afterload increases and preload is reduced. Stroke volume is decreased.[73] The cardiac output may be decreased or unchanged depending on the HR change. Systemic BP may increase towards the end of apnea, presumably due to the hypoxic stimulus and subsequently sympathetic vasoconstriction.[71,74] An abrupt increase of BP at the termination of apnea has consistently been demonstrated in almost all the studies. Despite a further reduction in stroke volume at the termination of the apnea,[68,71] the increased HR and abruptly increased peripheral vascular resistance (as high as 70%)[75] lead to a BP surge which mainly appears to be sympathetically mediated.[76]

Cerebral blood flow increases progressively during OSA followed by abrupt decrease after resumption of breathing.[77] Arterial partial pressure of CO_2 has been proposed to provide the main contribution to this fluctuation but elevated BP during the post apnea phase may also play a role.[78] Transient elevations of pulmonary artery pressure has also been reported in OSA patients,[65] especially during REM sleep.[66,79]

Hedner et al. were the first to demonstrate cyclical changes in sympathetic nerve activity in OSA (Figure 2).[80] MSNA increased progressively towards the end of apnea in response to hypoxia.[81] There was an abrupt decrease after termination of the apnea presumably as a result of increased vagal afferent input during post apnea hyperventilation[82] and baroreflex inhibition induced by the postapneic BP surge.

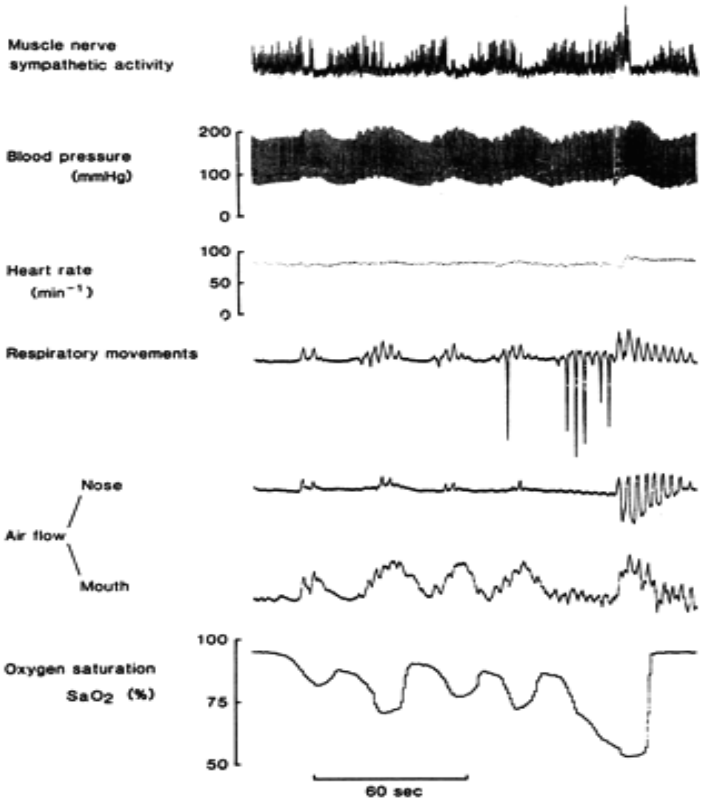

Figure 2. A typical recording of repetitive OSA and oscillation of BP and MSNA (adapted from Hedner et al. J Hypertens 1988).[80]

1.2.8 Clinical presentation and diagnostic criteria of OSA

The most common symptoms of OSA are snoring, witnessed apnea or gasping, excessive daytime sleepiness and non-restorative sleep. Other nighttime symptoms include choking, restless sleep, awakening with heart burn due to esophageal reflux, dry mouth and nocturia. Headache, fatigue, concentration difficulties and sexual dysfunction are also frequently reported by OSA patients.

Medical history and comorbidity are important for the diagnosis of OSA. OSA is overrepresented in people with Down syndrome, polycystic ovarian syndrome, depression, hypothyroidism, acromegaly or craniofacial disorders such as retroposed mandible. Other predisposing factors include adenotonsillar hypertrophy, a history of tonsillectomy and nasal problems (e.g. septal deviation). Comorbidities including obesity, hypertension, CV and metabolic disease are common in OSA patients.

Upper airway resistance syndrome is defined by repetitive upper airway obstruction resulting in inspiratory flow limitation and subsequent arousals from sleep.[83] It has been recognized as a sleep related respiratory disorder with a pathophysiology similar to OSA.[29] However, oxygen desaturation is not regularly seen in patients with upper airway resistance syndrome. These patients are more likely to report chronic insomnia, parasomnia, fatigue and have somatic complaints such as muscle pain.

The clinical diagnostic criteria of OSA in adult are summarized in Table 3.

Table 3. OSA diagnostic criteria adapted from the International Classification of Sleep Disorders.[29]

	Diagnostic criteria
A. At least one of the following applies: 1. Complaints of unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue or insomnia 2. Wake with breath holding, gasping or choking 3. Witnessed loud snoring and/or breathing interruptions during sleep	**A**, **B** and **D**
B. PSG recording shows the following: 1. Respiratory disturbance index (RDI, including apnea, hypopnea and RERA) five or more per hour of sleep 2. Evidence of respiratory effort during all or a portion of each respiratory event	Or **C** and **D**
C. PSG recording shows the following: 1. RDI fifteen or more per hour of sleep 2. Evidence of respiratory effort during all or a portion of each respiratory event	
D. The disorder is not better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder	

1.2.9 Questionnaires and diagnostic techniques in OSA

Anthropometric data, medical history, clinical symptoms (e.g. sleepiness) and quality of life questionnaires provide valuable information on functional impact of OSA patients and aid in making a clinical diagnosis. The Berlin Questionnaire is commonly used for OSA prediction.[84] Three domains focusing on persisting snoring behavior, daytime sleepiness, and hypertension/obesity history are included in the questionnaire. A patient fulfilling high risk criteria in at least two categories is classified at high risk of OSA. Epworth Sleepiness Scale (ESS) is the most widely used questionnaire for daytime sleepiness assessment.[85] Eight specific situations of daily life concerning sleepiness are scored from 0 to 3. An ESS score of more than 10 is usually considered suggestive of subjective daytime sleepiness. The Functional Outcome of Sleep Questionnaire could be used to estimate the functional impact on daily activity in disorders with daytime sleepiness (e.g. OSA).[86] Five factors (activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcome) are included in the questionnaire.

The sleep diagnostic test can be run in-lab or in the home environment. The ambulatory setting does not occupy the hospital bed, but the opportunity for intervention during the study is lost. The gold standard for diagnosis of OSA is in-laboratory attended PSG[87] which measures both sleep structure and respiratory disturbance events with low failure rate. With a proper protocol, ambulatory PSG can be used in clinical and research settings with reasonable success rate and signal quality.[88,89] On the other hand, OSA is highly prevalent and many patients remain undiagnosed. PSG requires technical expertise and is considered expensive and time-consuming. As a consequence, limited-channel portable monitoring (PM) devices have been applied for OSA diagnosis. The use of a PM device is considered to be a safe, reliable and economical procedure in the clinical routine although comprehensive patient evaluation and manual review of the raw data is crucial for a valid diagnosis. Based on the collected parameters and the study condition, devices for sleep studies have been subclassified into 4 categories according to the AASM (Table 4).[90]

1.2.10 Clinical consequences of OSA

1.2.10.1 Daytime sleepiness and quality of life

Patients with OSA frequently exhibit symptoms of excessive daytime sleepiness which may be reflected in subjective questionnaires (e.g. ESS, Stanford Sleepiness Scale[91]), by objective assessments like the Multiple Sleep Latency Test[92] and the Maintenance of Wakefulness Test.[93] Sleep fragmentation is

Table 4. AASM classification for diagnostic equipment.[90]

Type of PM device	Parameters measured
Type 1: Full attended PSG in a laboratory setting	Minimum 7 channels including EEG, EOG, chin EMG, electrocardiogram, airflow, respiratory effort and oxygen saturation
Type 2: Full unattended PSG	Minimum 7 channels including EEG, EOG, chin EMG, electrocardiogram or HR, airflow, respiratory effort and oxygen saturation
Type 3: Modified portable sleep apnea testing	Minimum 4 channels including ventilation or airflow (at least two channels of respiratory movement, or respiratory movement and airflow), HR or electrocardiogram, oxygen saturation
Type 4: Continuous single- or dual- bio parameter recording	One or two channels, typically including oxygen saturation or airflow

considered to play an important role in the development of sleepiness.[94,95] The biochemical mechanisms responsible for sleepiness development are incompletely known. However, modulators like interleukin-6 and tumor necrosis factor (TNF)-α have been linked to daytime sleepiness in OSA patients.[96] In a small placebo-controlled study of hypersomnolent OSA patients, etanercept (a TNF-α antagonist) reduced interleukin-6 concentration and increased sleep latency assessed by multiple sleep latency test.[97]

It has been estimated that 33% of OSA patients experience psychiatric illness and up to 80% have various degree of functional impairments.[98] Patients with severe OSA have poor quality of life equivalent to other chronic disorders (e.g. hypertension, type 2 diabetes) in the U.S. general population.[99] In the Wisconsin Sleep Cohort Study, OSA defined as AHI ≥5 was independently associated with lower general health status.[100] Similar findings have also been demonstrated in disease specific measures (e.g. Functional Outcome of Sleep Questionnaire).[86] However, whether there is a linear relationship between OSA severity and components of quality of life is still unclear.

1.2.10.2 Neuropsychological dysfunction and traffic safety

There is evidence suggesting that OSA patients exhibit variable degree of cognitive and performance deficits. Using an extended test battery, 95% of severe OSA patients were found to have an impaired vigilance and/or attention

compared with controls.[101] However, many studies in this area are hampered by the wide range of tests applied and the lack of normative data. In a meta-analysis of neuropsychological function in OSA patients, 10 outcome domains were coded and compared with referenced/normative data. Vigilance and executive function were markedly affected in OSA while intelligence and verbal ability appeared to be intact. Inconsistent results were reported for memory, visual and motor skill.[102]

Excessive sleepiness and performance decrement[103,104] increase the risk of traffic accidents in OSA patients.[105] Studies using state driving records[106,107] or self-reported crashes[108,109] have shown approximately 1.5 fold higher risk for motor vehicle collisions in OSA patients compared with controls.[110] A case-control study involving 102 drivers after traffic accident and 152 controls from local primary care center showed an odds ratio of 6.3 for having a traffic accident in patients with an AHI $\geq$10.[111]

1.2.10.3 Cardiovascular disease

Pathophysiological links between OSA and CV disease

The pathophysiological mechanisms involved in the development of CV disease in OSA have been extensively studied. Multiple pathways including neurohumoral activation,[112] oxidative stress[113] and inflammation[114] have been proposed. Some of these as well as other mechanisms are listed in Table 5.

Hypertension

Data from large cross-sectional[34,115] and population-based longitudinal[116] studies provide strong evidence for a severity-dependent relationship between OSA and hypertension. OSA has been identified as one of the causes for development of secondary hypertension in the JNC 7th report.[117] A recent large prospective study in a middle-aged and older group did not find that AHI predicts hypertension after adjusting for obesity[118] although cross-sectional data from the same cohort revealed an association.[119]

It is well established that continuous positive airway pressure (CPAP) can eliminate the BP surges associated with apneic events during sleep. This attenuation may act to restore the normal nocturnal "dipping pattern"[120] which frequently is lacking[121] in OSA patients. Using conventional clinical BP measurement, a substantial reduction of daytime systolic and diastolic BP was demonstrated in obese male OSA patients after CPAP.[122] Others only found a

Table 5. Mechanism for development of CV disease in OSA.

Potential pathway mechanism	Evidence	Effect of CPAP treatment
Sympathetic nerve activity	MSNA increased during sleep and wakefulness[80,123]	MSNA reduced[124]
Neurohumoral control of circulation	Plasma[124] and urinary[125] norepinephrine increased Plasma angiotensin II increased[126]	Plasma[124] and urinary[127] norepinephrine decreased Plasma angiotensin II decreased[126]
Carotid chemoreflex function	Sensitization and potentiation of the carotid chemoreceptor in response to peripheral chemoreceptor activation[128,129]	
Baroreflex function	Reduced baroreflex control[130]	Improved baroreflex function[131]
Local vascular regulation	Reduced bioavailability of nitric oxide[132,133] Impaired endothelial dependent vascular dilation[134,135] Reduced pulmonary artery nitric oxide release[136] Impaired norepinephrine induced vasoconstriction[137] Enhanced angiotensin II induced vasoconstriction[138]	Increased serum nitrite/nitrate levels[132,133] Improvement of endothelial dependent vascular dilation[139-141] Enhanced response to L-NMMA in pulmonary circulation[136]
Inflammation	Elevated C-reactive protein concentration[142,143] Increased interleukin-6 concentration[143] Increased TNF-α concentration[144]	Reduction of C-reactive protein concentration[143] Reduced interleukin-6 concentration[143] Reduced TNF-α concentration[144]
Structural vascular change	Increased intima-media thickness[145-147] Increased arterial stiffness[148,149]	Reduced intima-media thickness[150] Reduced arterial stiffness[150,151]

Development of atherosclerosis	Increased serum amyloid A [152] Functional change of CD8+ T-lymphocytes[153] High density lipoprotein (HDL) dysfunction[154] Increased soluble CD40 ligand concentration[155] Increased nuclear factor kappa B concentration[156] Delayed neutrophil apoptosis[157] Increased leukotriene B4 concentration[158] Elevated circulating cell-derived microparticles[159]	 Improved CD8+ T-lymphocytes function[153] Reduced soluble CD40 ligand level[155] Reduced nuclear factor kappa B level[156]
Development of thrombosis	Enhanced platelet activation and aggregation[160,161] Enhanced erythrocyte adhesiveness and aggregation[162] Increased fibrinogen concentration[162-164] Reduced fibrinolytic activity[165] Increased endothelial cell apoptosis[166]	Reduced platelet aggregation[160,161] Fibrinogen concentration decreased[163]
Cardiac functional change and ventricular remodeling	Diastolic dysfunction[167,168] Interatrial shunting in patients with patent foramen ovale[169,170] Increased left ventricular mass[149,171]	

modest change on diastolic BP in mild to moderate OSA[172] or no change on BP[173]. Evidence of a beneficial effect on 24-hour BP after CPAP is also emerging though some uncertainty remains. A modest but significant reduction

of mean 24-hour BP was demonstrated in some randomized controlled studies[174-177] but not others[178-185]. The BP response to CPAP in OSA patients may associated with apnea severity,[176] baseline BP level,[186,187] baseline BMI,[187] presence of daytime sleepiness,[180,183] or improvement of excessive daytime sleepiness[187]. OSA is frequently associated with masked hypertension[188] and drug-resistant hypertension[189]. CPAP treatment may reduce daytime and nocturnal BP in refractory hypertension patients.[120,190] However, BP lowering agents remain the mainstay treatment for BP control in hypertensive patients with OSA.

Coronary artery disease (CAD)

OSA was reported to be prevalent in patients with CAD and has been independently associated with CAD after adjusting for traditional risk factors.[191] This association was proportionally weak in a large cross-sectional population-based study including an older population.[192] A study using coronary artery calcification as the indicator of subclinical atherosclerosis demonstrated an independent association between the presence and severity of OSA and coronary artery calcification in a group of patients without a history of CAD.[193]

Apneic events during sleep could reduce myocardial oxygen delivery and increase myocardial oxygen demand by chronotropic stimulation. This may have deleterious effects on unstable coronary lesions, plaque rupture and thrombogenesis. CPAP treatment has been shown to improve nocturnal angina in OSA patients with coexisting CAD.[194,195]

Cardiac arrhythmias

Cardiac arrhythmias are common among OSA patients. Sinus arrest, sinus bradycardia, atrioventricular block, atrial fibrillation/flutter and nonsustained ventricular tachycardia were detected in nearly 50% of patients with severe OSA in an early study.[196] This finding was further supported by evidence from a population-based study showing that severe OSA patients had a two to four fold higher risk for complex arrhythmias compared with non-OSA even after adjustment for potential confounders.[197] In a cross-sectional analysis, Gami and colleagues reported that OSA patients with sudden death had a markedly higher rate of fatal cardiac events during sleeping hours (midnight to 6:00 am) compared to those without OSA.[198] Others have found nocturnal bradyarrhythmia is associated REM sleep[199] and OSA severity[200]. Treatment of OSA reduced the occurrence of nocturnal cardiac rhythm disturbances.[196,201-204] Patients with untreated OSA had an increased risk for recurrence of atrial fibrillation after cardioversion.[205]

Congestive heart failure

Data from a large population-based cohort have suggested an association between OSA and congestive heart failure.[192] However, strong evidence for OSA as a cause of congestive heart failure is still lacking. Left ventricular systolic dysfunction defined as left ventricular ejection fraction <50% was observed in 7.7% of the OSA patients in a prospective clinical cohort.[206] Left ventricular diastolic dysfunction was found in 25 out of 68 severe OSA patients which was predicted by minimum oxygen desaturation <70%.[168] Left ventricular mass index was found to be 15% higher in normotensive OSA patients compared with controls[171] and the magnitude of left ventricular hypertrophy in sleep apnea patients was reported to be similar to hypertensive patients without OSA.[149] However, in patients with obesity, OSA was found to be associated with depressed diastolic function and increased left atrial volume rather than left ventricular hypertrophy.[207]

Pulmonary hypertension

The pulmonary artery pressure was elevated in OSA patients compared with matched controls.[184] A structural change of the pulmonary vascular bed leading to chronic elevation of pulmonary artery pressure may be a consequence of repetitive pulmonary artery pressure increases during apneic events. The prevalence of OSA related pulmonary hypertension has been estimated at 20% in the absence of pulmonary disease.[208] Additionally, OSA patients may exhibit pulmonary hypertension during exercise even if the pulmonary artery pressure is normal at rest.[209] CPAP treatment has been demonstrated to decrease daytime pulmonary artery pressure regardless of the presence of pulmonary hypertension.[184,210,211]

Stroke

OSA has been linked to stroke in a cross-sectional population-based study.[192] Severe OSA was associated with increased risk of ischemic stroke over the next 6 years in an elderly population (hazard ratio 2.52).[212] An independent association between moderate to severe OSA (AHI ≥20) and prevalent stroke was demonstrated in a cross-sectional analysis of the Wisconsin sleep cohort.[213] However, the odds ratio was no longer significant after adjustment for confounders in a four-year follow-up prospective analysis. OSA, defined by AHI ≥10, has also been independently associated increased cerebrovascular events in patients with CAD.[214]

Stroke may also be a factor behind the development of SDB, although the main body of evidence suggests that obstructive events forgo the development of stroke. In a prospective study of stroke and transient ischemic attack patients,

the frequency of obstructive events was unchanged between the hospital admission and 3-month follow-up while central events reduced at stable phase compared to acute phase.[215]

CV mortality and all-cause mortality

Data from an early uncontrolled study[216] and a recent longitudinal study[217] suggested that OSA is associated with increased risk for development of CV disease which could be reduced by treatment. Other long term follow-up studies also provide compelling evidence on the relationship between OSA and CV mortality. Yaggi et al. reported that OSA (AHI ≥5) was significantly associated with stroke or death (hazard ratio 1.97) independent of other traditional CV risk factors including hypertension.[218] In a 10-year follow-up study, Marin and colleagues found that patients with untreated severe OSA had a 2-fold increased risk of both CV death and non-fatal CV events compared with healthy controls, and CPAP treatment reduced this risk.[219] In the community-based Busselton health study, moderate-to-severe OSA was independently associated with a large increased risk of all-cause mortality after 13 years (hazard ratio 6.24).[220] Similar results have been demonstrated in the 18-year follow-up of the Wisconsin sleep cohort.[221] The adjusted hazard ratio for severe untreated OSA versus non-OSA for all-cause mortality and CV mortality was 3.8 and 5.2, respectively. This risk scenario may be extended as the Kaplan-Meier survival curve in this study demonstrated that at least ten years of follow-up elapsed prior to the acceleration of mortality rate in middle-aged OSA patients.

1.2.10.4 Insulin resistance

Sleep apnea has been considered as a manifestation of the metabolic syndrome.[222] The combination of OSA and other traditional components of the metabolic syndrome has been labeled as the "syndrome Z".[223] Insulin resistance, a central containment of the metabolic syndrome, has been associated with OSA in clinic-based[224,225] and community-based[226,227] studies. A cross-sectional analysis of the Wisconsin sleep cohort revealed high prevalence of type-2 diabetes in patients with moderate to severe OSA (AHI ≥15) compared to non-OSA. However, a 4-year follow-up did not find significant increase risk of diabetes development after adjustment for age, sex, and body habitus.[228]

The potential mechanism linking OSA and insulin resistance is still not fully understood. However, intermittent hypoxia and sleep fragmentation caused by OSA may have an impact on several organ systems and cellular processes that potentially could lead to insulin resistance (Figure 3).

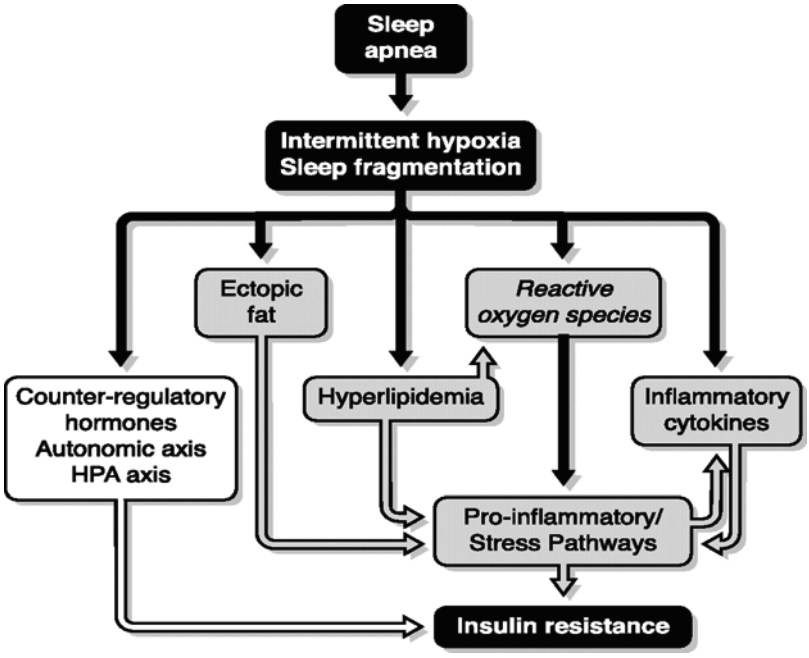

Figure 3. Putative scheme illustrating pathways by which intermittent hypoxia and sleep fragmentation could cause insulin resistance through activation of "classical" (white) or "lipotoxic" (grey) pathways. Dempsey et al. Physiol. Rev. 2010 used with permission.[229]

A potential effect of CPAP treatment on insulin sensitivity has been showed in some[230-232] but not all[122,233-236] studies in patients with OSA. Differences in sample size, patient selection, treatment duration and CPAP compliance may at least in part explain the discrepancies between the studies.

1.2.10.5 Lipid metabolism and liver function

The association between dyslipidemia and OSA has recently been studied extensively. In the Sleep Heart Health Study, HDL was found to be inversely related to AHI in women and men aged below 65 years. Triglycerides were only associated with AHI in subjects less than 65 year old. Total cholesterol did not vary across the AHI span.[237] Moderate to severe OSA was associated with low HDL serum levels independently of gender, BMI, hypertension, glycaemia and treated dyslipidemia in an elderly population.[238] In a case-control study, total cholesterol and low density lipoprotein was higher in OSA patients compared

with controls.[239] Other cross-sectional studies could not confirm these differences.[154,240] In a non-randomized study, six-month treatment with CPAP was associated with a 15% increase in HDL, 17% decrease in low density lipoprotein.[234] Similar findings were reported in a randomized controlled study including 220 patients.[241] Total cholesterol decreased significantly after one-month of CPAP treatment. The magnitude of the effect on lipid status was calculated to correspond to a reduction of CV risk by 15%.

The serum aminotransferase concentration has been proposed as a hypoxia marker in OSA.[242] A single night with CPAP reduced the nocturnal rise of aspartate aminotransferase and alanine aminotransferase in obese OSA patients.[243] However, a recent randomized controlled study that applied sham-CPAP could not confirm this effect after four weeks of treatment.[244]

The combination of OSA, obesity and insulin resistance has been proposed to accelerate the development of non-alcoholic fatty liver disease[245] by a mechanism potentially involving hypoxia.[246] A recent study by Polotsky and coworkers implied that hypoxic stress caused by apnea may induce insulin resistance and steatohepatitis in patients with severe obesity.[247]

1.2.11 Treatment of OSA

OSA is a chronic condition that requires long-term, multidisciplinary approaches. Besides treating OSA events during sleep, multiple components need to be implemented into the treatment strategy. These include the practice of proper sleep hygiene, weight loss in overweight/obese patients, avoidance of factors that worsen disease, adherence to therapy, and attention to OSA specific quality of life factors.[248]

1.2.11.1 Behavioral treatment

OSA patients should be advised to stop smoking and to avoid alcohol and sedatives before bedtime. Supine position is known to impact upper airway size and patency, especially in the lateral dimension[249]. And more severe OSA is generally seen in the supine position.[250] Positional therapy may be applied in many patients, especially for those with position-dependent OSA.[251]

1.2.11.2 Positive airway pressure

CPAP was first described by Sullivan et al. in 1981[252] and has been the mainstay of OSA treatment since then. CPAP induces a pneumatic splint in the

upper airway and prevents the airway collapse. Whether CPAP could affect upper airway patency through increase lung volume is still unclear.[253,254]

The treatment effect of CPAP on nocturnal SDB is dramatic. The absolute usage of CPAP is directly correlated with improvement of subjective/objective daytime sleepiness and quality of life.[255] However, the acceptance of CPAP is variable and the adherence to CPAP is frequently suboptimal. An average 4-hour CPAP usage per night is currently used to define acceptable use in most sleep clinics. Modified techniques like autotitrating CPAP, pressure-relief CPAP and Bi-level positive airway pressure have been developed with the aim to lower administrated pressure, increase functionality, and increase comfort in positive pressure therapy users. In general, these devices provide similar treatment effect to conventional CPAP on OSA. However, they may improve the compliance in some cases. Side effects including nasal congestion and rhinorrhea are not uncommon in CPAP users. Humidification may be helpful to treat nasal dryness.

1.2.11.3 Mandibular advancement device

Custom made mandibular advancement device may be used to treat mild to moderate OSA in patients who do not tolerate CPAP or prefer such devices in front of CPAP.[256] Mandibular advancement device improves upper airway patency during sleep by enlarging the upper airway and decreasing upper airway collapsibility.[257] These devices typically cover the upper and lower teeth and maintain the mandible in a forward and downward position with respect to the resting state. A meta-analysis study demonstrated that oral devices reduce AHI by approximately 11 events/hour compared with placebo and are less effective than CPAP.[258] However, a randomized controlled crossover trial comparing a three-month treatment with oral device and CPAP found an equal reduction of symptoms and subjective sleepiness.[182] Moreover, oral devices may have some beneficial effects on BP in patients received the treatment.[182,259] The side effects of the oral device include increased salivation or dryness, tender teeth and jaws, but they are considered negligible.

1.2.11.4 Surgical treatment

As the early treatment option for OSA, tracheostomy was first described by Kuhlo et al. in 1969.[260] This technique is evidently limited by its clinical complications. Uvulopalatopharyngoplasty was later introduced as a surgical procedure to treat OSA,[261] however, it appeared to be insufficient.[262] Other upper airway reconstructive procedures (e.g. maxillary and mandibular

advancement) have been applied in a limited group of patients with OSA.[263] These procedures may improve clinical outcomes but have not been proven curative for OSA in general.

1.2.11.5 Weight reduction management

Weight reduction has convincingly been demonstrated to reduce SDB in obese patients with OSA. In a longitudinal study evaluating association between moderate weight change and change in OSA severity, 1% decrease in body weight was associated with a 2.6% decrease in AHI.[41] Hence, lifestyle and diet changes are strongly recommended for overweight and obese OSA patients.

Bariatric surgery is frequently used to achieve major weight loss in patients with a BMI ≥40 (or BMI ≥35 in combination with important comorbidities) who fail weight control after conventional methods.[264] It may also be considered as an adjunct treatment for OSA in morbidly obese patients.[265] A meta-analysis of 136 studies with 22,000 patients suggested that OSA improved in 85.7% of patients following the surgery.[266]

Drug-assisted weight reduction may provide an alternative mean to reduce the severity of OSA. An open, uncontrolled cohort study of sibutramine (a serotonin and noradrenaline reuptake inhibitor) in 87 obese men with OSA resulted in approximately 8.5% body weight loss after 6 months. This change was accompanied by a 35% reduction in SDB (RDI from 46 to 30 events/hour).[267] Favorable metabolic and body composition changes were found in addition to AHI reduction after sibutramine in combination of diet and exercise in 93 patients with moderate to severe OSA.[268] However, these findings were not confirmed in a recent uncontrolled study administrating sibutramine for 12 months.[269]

1.2.11.6 Pharmacological treatment of OSA

Several pharmacologic agents have been attempted in OSA. These include among others serotonergic and serotonin receptor antagonist drugs, cholinesterase inhibitory agents, carbonic anhydrase inhibitors, a glutamate antagonist and nasal decongestants.[270] However, none of these agents have proven consistent efficacy.

Modafinil is widely used to treat residual excessive sleepiness after CPAP treatment in OSA patients. Several randomized and placebo-controlled trials have demonstrated that modafinil improves subjective and objective daytime

sleepiness, vigilance and quality of life in these patients.[271-273] However, modafinil has no effect on the occurrence of OSA.[274] Reduced CPAP compliance[275] and a mild increase of BP[276] have been associated with the therapy, which needs to be closely monitored. Armodafinil, the R-enantiomer of racemic modafinil, was found to have similar effects on residual daytime sleepiness in CPAP-adherent OSA patients.[277,278]

1.2.11.7 Other therapeutic approach

Oxygen supplementation can reduce nocturnal hypoxia in patients with OSA. However, it may also prolong the time to arousal from an apenic event, increase apnea duration, thereby causing hypercapnia.[279] CO_2 has been used as an adjunctive therapy to CPAP for the treatment of refractory mixed central and obstructive SDB in a small study.[280] Atrial overdrive pacing was reported to reduce CSB and OSA in a small group of patients.[281] However, it could not be replicated by others.[282-284] Electrical stimulation of the genioglossus muscle has been shown to reduce upper airway resistance.[285] Apnea triggered neuromuscular stimulation via a pacing device was found to reduce apnea and severe oxygen desaturation events during sleep in a small study of six patients.[286] Tongue muscle training was found to reduce snoring but not AHI in severe OSA patients.[287] Interestingly, patients with moderate OSA were studied in a randomized controlled trial of didgeridoo playing.[288] Four-month of training reduced AHI and subjective sleepiness although there was no change in health related quality of life.

1.3 Peripheral arterial tone

1.3.1 Regulation of finger skin microcirculation

Like other extremities, the finger skin vascular beds are rich in arteriovenous anastomoses amounting to approximately 500/cm^2 in the finger nail beds.[289] Arteriovenous anastomoses are coiled vessels with thick, muscular, and densely innervated walls connecting the arterioles and venules in the dermis. Blood from the digital artery bypasses the high-resistance arterioles and the capillaries of the papillary plexus, flows directly through the dermal arteriovenous anastomoses and returns to the deep plexus of veins. This special feature enables large variations of digital skin blood flow which ranges from 1 to 90 ml/min/100ml of tissue.[290] This vascular bed accounts for the majority of total digital blood flow.[291]

The finger vascular bed is highly innervated. Despite local factors affecting finger blood flow, the microcirculation in the digital skin vascular bed is mainly controlled by the systemic vasoconstrictor tone.

1.3.2 Finger blood flow and finger plethysmography

Many techniques have been used for the assessment of finger microcirculation including radioisotope clearance, capillaroscopy, laser Doppler flowmetry and finger plethysmography. Finger plethysmography is a non-invasive method measuring the changes in finger volume. Blood flow changes obtained by venous occlusion have been closely correlated with pulse volume changes measured by finger plethysmography in early studies.[290,292]

1.3.3 Finger pulse wave form

Finger pulse wave form is the pulsatile signal derived from the finger plethysmography. It represents the increase of blood volume in the finger vascular bed which is corresponding to each heart beat.[293] Pulse wave amplitude (PWA), the foot to peak amplitude of the pulse wave form, is one of the most frequently used parameters in the analysis. It has been shown elegantly by Bini et al. that finger PWA is associated with median nerve bursts during a cooling test (Figure 4).[294] Using a daytime infusion protocol, Grote and colleagues found that PWA derived from the fingerplethysmography was sensitive to the α-receptor agonist norepinephrine but not to the β_2–receptor agonist isoproterenol.[295] It was concluded that finger PWA, as a measure of digital skin blood flow, may serve as a marker of generalized sympathetic nerve activation in this local vascular bed.

1.3.4 Peripheral arterial tone technique

Peripheral arterial tone (PAT) is a novel technology for finger plethysmographic measurement that records pulsatile arterial volume signals in the finger using a pressure-applied optical probe. It was first introduced to the sleep medicine field as a marker of OSA by Schnall et al. in 1999,[296] and later used as a portable device (Watch_PAT100, [WP100]) for OSA diagnostics.[297] In addition, the PAT technique has been applied to study patients with CV disease[298] and endothelial dysfunction[299] in daytime function test.

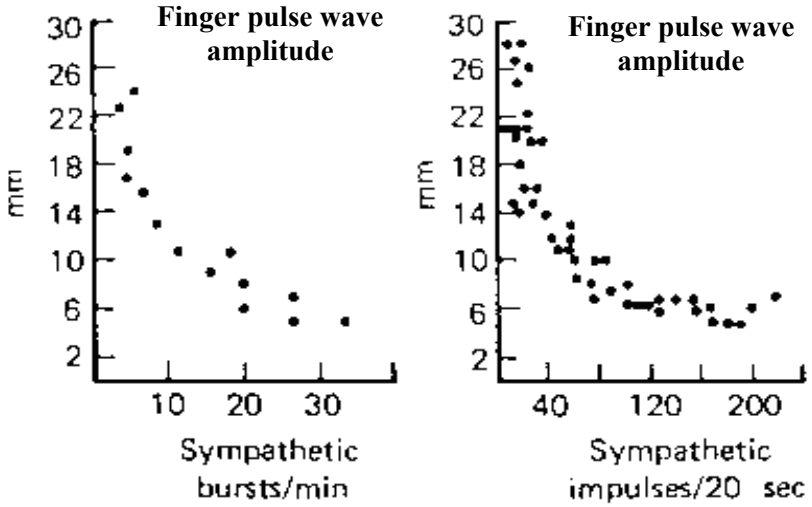

Figure 4. Quantitative relationship between median nerve burst and finger pulse amplitude during temperature changes (adapted from Bini et al. J Physiol. 1980).[294]

1.3.4.1 PAT probe design features

The PAT probe is an elongated, longitudinally split thimble, completely lined with a highly compliant elastic membrane surrounded by an outer rigid casing (Figure 5a). Compared to conventional finger plethysmography, several features are implemented to assure accurate and comfortable measurement of finger arterial volume changes over an extended period.[300]

First, a full-length, uniform pressure anti-venous pooling region is used to cover the surface of the distal end of the finger. The external counter-pressure inhibits venous blood pooling/distension and prevents the induction of veno-arteriolar reflex vasoconstriction.[301] The split thimble design of the PAT probe allows generating fixed level of pressure irrespective of the size of the finger. When the finger is inserted into the probe, a proportionate amount of air is shifted from the inner compartment of the probe to its outer compartment, causing the pre-tensioned outer membrane to be pushed off the wall of the inner shell and applying pressure to the air within the probe (Figure 5b). The elastic properties of the balloon like outer membrane creates a constant pressure within the range of normal finger size (Figure 6). Moreover, by applying substantial external counter pressure, the PAT probe produces an unloading of arterial wall tension,

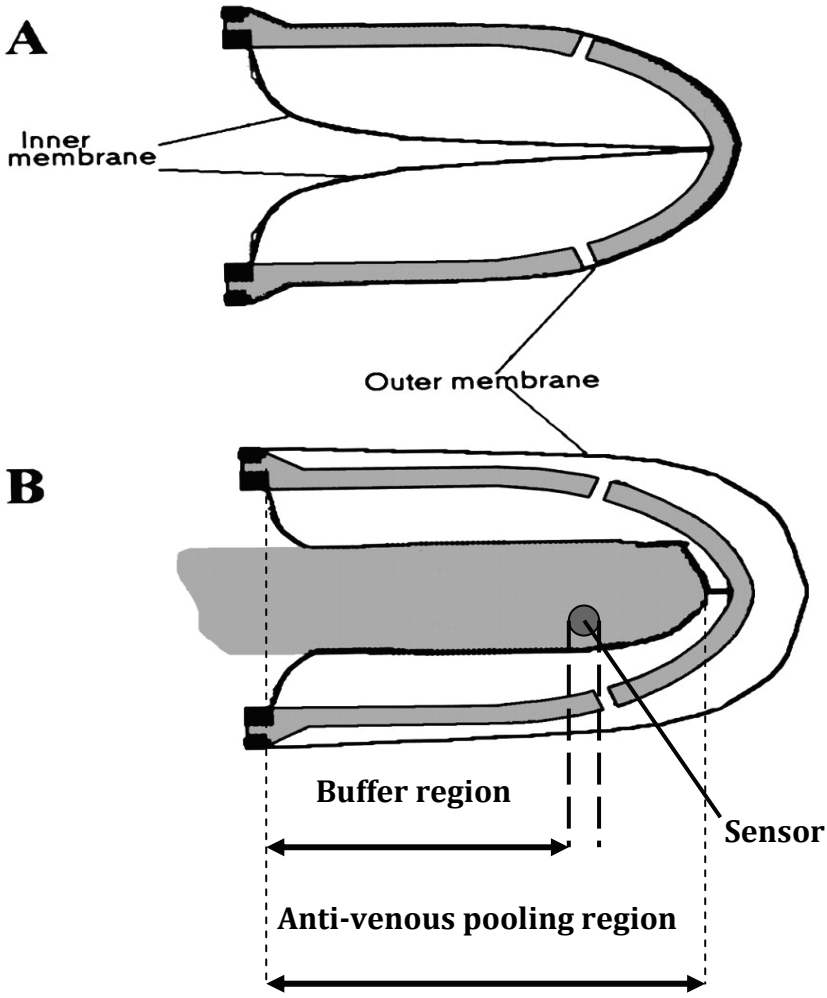

Figure 5a and **5b.** Cross-sectional view of the pneumo-optical PAT finger probe, insertion tabs and external probe cover are not shown (adapted from Bar et al. Chest 2003).[297]

thereby increases the arterial wall motion and the size of the arterial volume change. An extended pressure field buffer region relative to the optical sensor could buffer the sensor region from retrograded venous blood perturbation, which is common during movement. In addition, the buffer region can immobilize the distal finger joint and help to eliminate the artifact caused by finger bending.

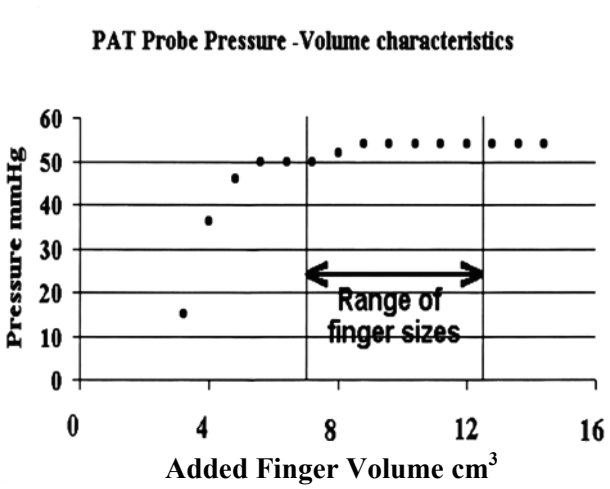

Figure 6. Pressure vs. added finger volume graph of the PAT finger probe (adapted from Bar et al. Chest 2003).[297]

1.3.4.2 Optical measurement of PAT

A transmission mode photoplethysmography is used to measure the optical density changes associated with pulsatile blood volume changes of the finger in the PAT probe. The sensor is situated at opposing lateral side of the middle of the distal phalanx (Figure 5b). The optical sensing method is highly correlated with volumetric measurement (Figure 7a, 7b) and provides a convenient and reliable surrogate measure for the volumetric change in the finger.

1.3.5 Other markers of sympathetic activity in sleep medicine

1.3.5.1 Heart rate variability

Heart rate variability is a useful tool for the assessment of autonomic nervous system function. The rhythmic contributions of sympathetic and parasympathetic nervous activity on HR can be distinguished in frequency domains using spectral analysis.[302] The high frequency (HF) (0.15-0.4 Hz) component, corresponding to respiratory modulation, is mainly controlled by parasympathetic activity. The low frequency (LF) (0.04-0.15 Hz) component is jointly controlled by vagal and sympathetic activity with a predominance of

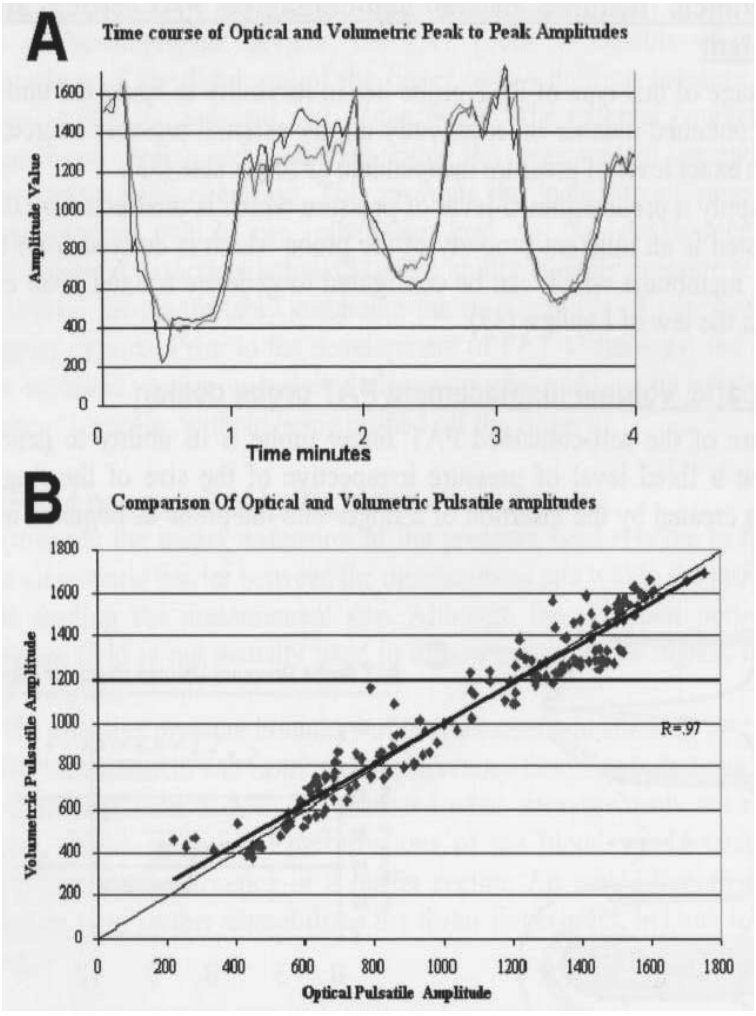

Figure 7a. Time-course of optical and volumetric signals recorded simultaneously from the same finger. Three reflex mediated episodes of vasoconstriction are shown. **Figure 7b.** Scatter plot of optical vs. volumetric signals show very high concordance and degree of linearity between signals (r^2 = 0.94). Used with permission from Bar et al. 2003.[300]

sympathetic influence. The LF/HF ratio is frequently used to reflect sympathetic vagal balance. It is important to note that conventional spectral analysis methods (e.g. fast Fourier transform) only can be applied to stable conditions. The applicability of heart rate variability analysis in patients with OSA is

therefore limited as a result of the periodic CV and respiratory changes. Nevertheless, by using a time-varying Wigner-Ville transform analysis, Spicuzza et al. found that HF oscillation was significantly higher during apnea compared with the postapneic hyperventilation period whereas the LF component was higher during the postapneic phase compared with apnea suggesting a surge in sympathetic activity after the obstructive apnea events.[303]

1.3.5.2 Pulse transit time

Pulse transit time (PTT) reflects the time interval for an arterial pressure pulse to propagate from the aortic valve level to a given peripheral site. PTT is often measured as the time lapsed from the appearance of the R wave in the electrocardiogram to the start of the pulse wave appearing in the finger oximetry recording. The PTT depends on the degree of stiffness of the arterial wall and is inversely related to arterial systolic BP.[304] During inspiration, the increase of thoracic cavity volume and the decrease of thoracic pressure lead to a decline of BP and an increase of PTT. The changes of PTT therefore can be applied as a surrogate quantitative measure of inspiratory effort in OSA patients[305] and to differentiate varies types of respiratory events (hypopnea, RERA and central events).[306,307] Transitory dipping in the PTT signal was reported to associate with EEG arousal[308] and was found to be as sensitive as a decrease in the finger PWA to detect arousals.[309] Several studies have shown that PTT can improve microarousal detection in children[310] and infants[311]. However, similar to PAT, this technique can sometimes be oversensitive for detection of arousal in children.[312] Artifacts in finger pulse wave form detection and interference caused by chest wall movement may also lead to misinterpretation of the PTT signal.[313] Finally, the usefulness of this method is limited in patients with cardiac arrhythmias, such as atrial fibrillation or extrasystolic activity.[314]

AIMS OF THIS THESIS

The objectives of this thesis were to

1. Characterize the role of adrenergic α-receptors in autonomic control of digital skin blood flow (reflected by the PAT signal) in response to obstructive apnea/hypopnea events (study I)

2. Compare the effect of doxazosin (DO, a peripheral a-receptor inhibitor) and enalapril (EN, an angiotensin-converting enzyme inhibitor) on digital vasoconstriction (measured by PAT attenuation) and nocturnal BP in hypertensive OSA patients (study II)

3. Validate a portable PAT device for OSA diagnostics using synchronized ambulatory PSG in the home environment (study III)

4. Assess the relationship between nocturnal PAT attenuation and daytime office BP in a population based cohort (study IV)

5. Develop and validate a pulse oximetry based autonomic state indicator (ASI) algorithm for CV risk assessment (study V)

METHODS

3.1 Study subjects

3.1.1 Sleep lab cohort (study I, II and V)

Subjects from study I, II and V were selected from patients referred to the sleep laboratory, Sahlgrenska university hospital, Gothenburg (for detailed information see Table 6). No gender criteria were specified in the study protocols. However, only male patients were recruited in study I and II.

Table 6. Characteristics of the study sample in study I, II and V.

Study	Number of the subjects	Inclusion criteria	Exclusion criteria	Study drop-out
I	8	Severe OSA patients without vasoactive medications	Smoker, peripheral vascular disease, diabetes mellitus, hypercholesterolemia	None
II	16	RDI ≥20 events/h; 140 mmHg ≤systolic BP ≤200 mmHg; 90 mmHg ≤diastolic BP ≤110 mmHg	Under OSA treatment; significant CAD, arrhythmia, stroke, heart failure and peripheral vascular disease	Two patients did not complete the study due to side effects (sweating and palpitation)
V	213	Randomly selected from patients referred for clinical investigation	None	Technical failure and/or insufficient signal quality (n=65)

3.1.2 Population based cohort (study III and IV)

Subjects in the study III and IV were selected from the Skaraborg Sleep Study[315] investigating a population based cohort screened in the Skaraborg Hypertension and Diabetes Project[316].

The Skaraborg Hypertension and Diabetes Project started in 1991 with the overall goal to improve BP control in the community and to assess the association between hypertension and type-2 diabetes with specific emphasis on

the interaction between lifestyle and genetics. The Skara primary health care centre is the only available public primary healthcare facility in Skara, a community with approximately 18,000 inhabitants. Practically all residents with hypertension, type 2 diabetes, or both hypertension and diabetes have been continuously surveyed (1992-1993), including annual follow-up visits at this center. The baseline examination included all patients with hypertension and diabetes (n=1149) in the community population. In parallel to this survey, an invitation was extended to 1400 subjects aged 40 years and older, stratified for age and sex, and randomly selected from the population census registry (1993-1994). From this control population, with an 80% response and participation rate, 1109 subjects attended the clinic for an investigation applying the same protocol as that used for the patient surveillance.

In the Skaraborg Sleep Study, a case-control design was used aiming for inclusion of 100 male and 100 female patients with hypertension from the surveyed population and a corresponding number of population controls previously classified as normotensive. Participants from the 2 cohorts, aged 40 to 65 years at baseline, were separately invited in random order to undergo an ambulatory full-night PSG recording. The final number of study participants is shown in Figure 8.

A subsample of 109 consecutive participants from the Skaraborg Sleep Study was further invited to undergo simultaneous WP100 and PSG recordings during the survey. Exclusion criteria (e.g. α-blocker medication, bilateral sympathectomy, Raynaud disease, acrocyanosis, vasculopathy, neuropathy, or autonomic nervous system dysfunction) were met by 3 subjects. Recordings from 106 subjects were included in the study III. Recording failures and computation problem due to data format incompatibility occurred in 25 cases, and 81 recordings were finally incorporated in the study IV.

3.2 Study design

Study I used an experimental intervention protocol, finger blood flow changes obtained during different dose levels of infused drug were compared. Study II was a double-blind crossover comparative trial with wash-out period between the treatments. Study III was a cross-sectional investigation using both correlation and receiver operating characteristic (ROC) analyses to validate WP100 versus ambulatory PSG. Study IV was a cross-sectional investigation using correlation and regression analyses to evaluate the association between PAT attenuation and office BP. Study V was based on cross-sectional analyses of patients referred to a sleep laboratory. An algorithm to predict CV risk from a

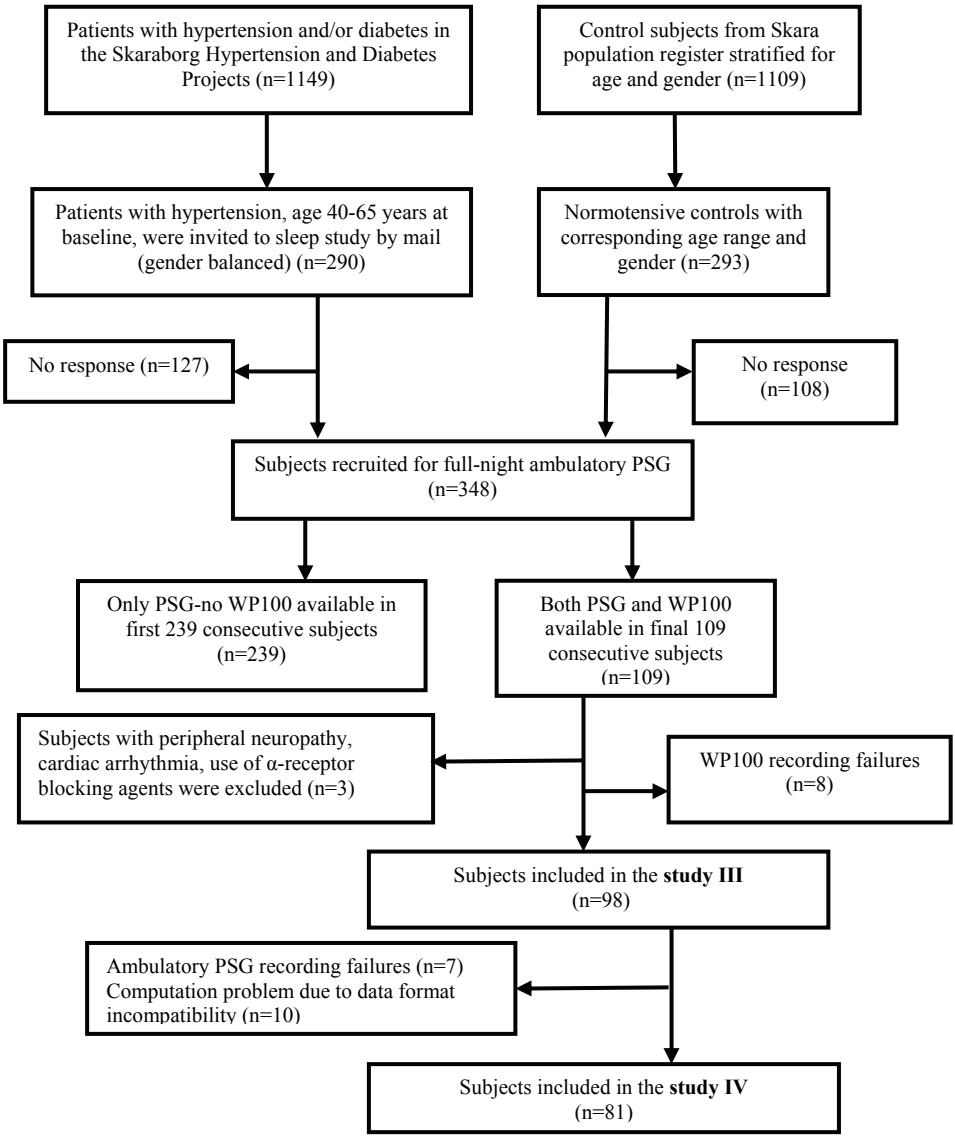

Figure 8. Flow chart displaying subject selection in study III and IV.

pulse oximetry signal using neuro-fuzzy system was developed and validated using multivariate logistic regression and ROC analyses.

3.3 Ethical considerations

All studies were approved by the Ethics Committee of the Medical Faculty of Gothenburg University. Informed consent was obtained from all the participants prior to the studies.

3.4 Interarterial infusion protocol (study I)

In study I, the combined α_1 and α_2 receptor antagonist phentolamine (Regitin®, Novartis, Switzerland) was infused via the brachial artery during sleep at three dose levels (0.066, 0.2 and 2 μg/min/100ml forearm volume). Each infusion step extended over 20 minutes. A minimum of 20 minutes sleep was allowed between each infusion step. An additional fourth dose of phentolamine corresponding to 5 μg/min/100ml forearm volume was added in the last three patients for 20 minutes in order to better distinguish a ceiling effect of the dose-response curve.

Baseline data collection and infusion procedures took place no earlier than after 30 minutes of continuous sleep and after the subjects had demonstrated a sustained pattern of repetitive obstructive apnea/hypopnea events. The protocol therefore aimed at undertaking all measurements according to an approximately similar real time basis, but slight deviations between individual recordings did occur due to variable time lapsed until sleep onset. Due to the escalating dosing procedure, intervention order was not randomized in the protocol.

3.5 Antihypertensive treatment (study II)

The effects of DO (Alfadil, Pfizer, USA) and EN (Renitec, Merck, USA) in hypertensive OSA patients were investigated in study II. A three-week washout period was applied for patients with ongoing antihypertensive medication. Patients were randomly assigned to receive two weeks of treatment with a lower dosage (DO 4 mg OD or EN 10 mg OD, respectively) and titrated to DO 8 mg OD or EN 20 mg OD during an additional period of two weeks. A three-week washout period was applied between the two treatment periods (Figure 9). The DO and EN dosages used in the study II were based on defined daily dosage (assumed average maintenance dose per day for a drug used for its main indication in adults) in Sweden.

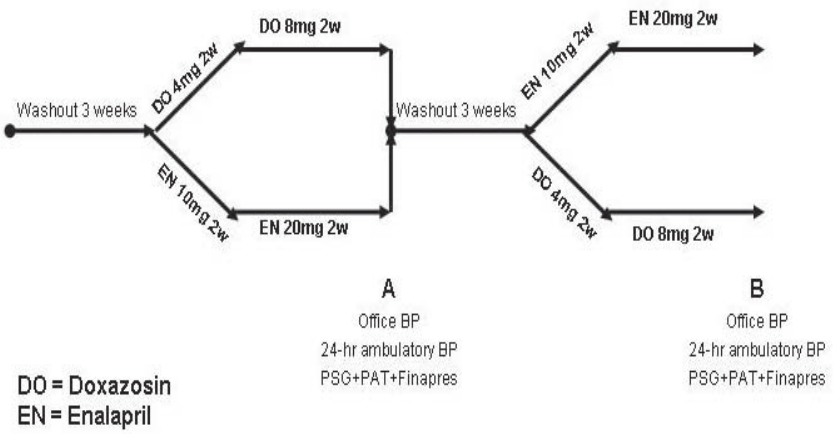

Figure 9. Flow chart of study II.

3.6 Anthropometric data and questionnaires

Body weight and height were determined to the nearest 0.1 kilogram and centimeter, respectively. BMI was calculated as weight in kilograms divided by the square of height in meters. Office BP was determined according to international standard[317] and measured in the supine position after a 5-minute rest using a cuff placed on the right arm at heart level. Systolic BP and diastolic BP were determined as the mean of three repeated measurements taken at 1-minute intervals. An ESS questionnaire was used in study II, III, IV and V. The Basic Nordic Sleep Questionnaire[318] was applied in study V.

3.7 BP monitoring

3.7.1 Intraarterial BP monitoring

In study I, a 20-gauge polyethylene catheter (Ohmeda, Swindon, UK) was inserted into the brachial artery of the non-dominant arm under sterile conditions. The catheter was connected to a DPT-6000 pressure transducer (PVB medizintechnik GMBH, Germany) and intermittently flushed with 0.9% saline using a three-port connector placed in series with the catheter transducer system. The intraarterial BP signal from the brachial artery was digitized at a

frequency of 100 Hz and continuously fed into the PSG system (Embla A10, Embla, USA).

The mean systolic/diastolic BP and pulse rate (PR) of the apnea/hypopnea event and the post apnea/hypopnea period were calculated at baseline and immediately after termination of phentolamine infusion, respectively. Mean arterial pressure (MAP) at each event/post-event period was calculated separately according to the formula MAP = (systolic pressure - diastolic pressure)/3 + diastolic pressure.

3.7.2 Beat-to-beat BP monitoring

It has previously been shown that beat-to-beat finger BP measurement closely reflects intraarterial BP during rest.[319] In study II, non-invasive beat-to-beat finger BP monitoring (Finarpres, Ohmeda, USA) was applied to continuously investigate the BP change during sleep. Finger BP signals were digitized at 100 Hz and fed into the PSG system. The mean overnight finger systolic and diastolic BP were used for the data analysis.

3.7.3 24-hour BP monitoring

In study II, 24-hour ambulatory BP monitoring was performed at the end of DO and EN treatment. BP was recorded with a cuff placed on the non-dominant arm at 20-min intervals during daytime (7:00–22:00) and 60-min intervals during night (22:00–7:00) in a single 24-h period using a portable BP monitor (Model 90207, SpaceLabs, USA). Patients were instructed to maintain their usual daily activity and sleep routines but to cease activity and keep the measurement arm still during readings. Average daytime BP and HR were calculated from their mean values from recordings obtained between 8:00 and 20:00. Nighttime parameters were calculated from their means between 24:00 and 6:00.

3.8 Sleep studies

3.8.1 PSG montage

The in-lab and ambulatory PSG recordings were performed using the Embla A10 system. The PSG recording montage consisted of three EEG channels (C_4/A_1, C_z/A_1, and C_3/A_2), left and right EOG, chin and anterior tibialis muscle EMG, and electrocardiogram. The ventilatory monitoring included nasal

cannula/pressure, oronasal thermistor, thoracic and abdominal respiratory-effort bands, body-position sensor, and finger pulse oximetry.

3.8.2 In-lab attended PSG

In-laboratory attended PSG recordings were performed in study I and II. In study I, patients underwent a single overnight PSG recording with minimum 6-hour sleep time in the laboratory. In study II, patients underwent two PSG recordings at the end of each treatment period (DO and EN, respectively).

3.8.3 Ambulatory PSG

Patients in study III and IV underwent a single night ambulatory PSG monitoring in the home environment. Electrodes and sensors were hooked up in the primary health care center between 6 pm and 9 pm. Impedance values were checked and electrodes were adjusted if paired impedances exceeded 5 kΩ. Standard calibrations were run by an experienced research nurse, and signals were visualized on a computer screen. Sensor positions were modified to optimize signal quality and secured by tape and net. Participants were instructed to go home and use the event button (lights off/on) for timing indications. The following morning, subjects were asked to complete a standard sleep diary (timing and quality). Equipment was removed by study nurses, and data stored in the memory card were downloaded to the computer using the PSG software Somnologica (Embla, USA).

3.8.4 Study V

In study V, the single night sleep data collection was based on clinical routine. Among the 213 subjects recruited in the study, attended and ambulatory PSG recordings were performed in 133 patients using Embla A10 system. Polygraphic recordings were performed in 80 patients with signals from thoracic and abdominal respiratory effort, nasal-oral airflow-pressure and body position (Somnocheck II, Weinmann, Germany).

3.8.5 PSG scoring

All the PSG recordings were manually scored according to international scoring criteria for sleep, breathing disorders, and arousal by technicians blinded to the studies.[5,6,320,321] An obstructive apnea/hypopnea event was defined as >50% amplitude reduction of airflow compared to baseline or an evident airflow

reduction associated with either an oxygen desaturation of >3% or an EEG arousal for at least 10 s in study I, II, III and IV.[320] Study V used the more recently adopted AASM manual for scoring of sleep and associated events. In brief, obstructive apnea was defined as a ≥90% decrease in airflow, with evident respiratory effort, lasting at least 10 seconds. Hypopnea was defined as a clear reduction of at least 50% airflow amplitude associated with an oxygen desaturation of ≥3% or an arousal.[6] The AHI was calculated as the total number of apnea and hypopnea events per hour of sleep. The oxygen desaturation index (ODI) was calculated as the number of oxygen desaturations of at least 4% per hour of sleep. The arousal index (ARI) was calculated as the number of arousals per hour of sleep.

For the polygraphic recording (study V), apnea was defined as ≥90% flow reduction compared to baseline for at least 10s. Hypopnea was defined as ≥50% nasal flow reduction with ≥3% desaturation from baseline for at least 10s. The AHI was calculated as the total number of apnea/hypopnea events per hour of total analysis time. The ODI was calculated as the number of oxygen desaturations of at least 4% per hour of analysis time.

3.9 PAT recording

3.9.1 Site PAT device

The site PAT device (Sleep PAT 200, Itamar, Israel) was used to record PAT signal in study I and II (Figure 10). The finger pulsatile volume signal was recorded via the PAT probe and electronically transferred to the site PAT device. The signal was subsequently band passed filtered (0.3-30 Hz), amplified, digitized with sampling frequency 100 Hz, and continuously fed into the PSG system (Embla A10).

3.9.2 Portable PAT device

The WP100 device (Itamar, Israel) was used for the PAT recordings in study III and IV (Figure 11). This is a battery-powered forearm-mounted consoled device with 2 finger-mounted probes, PAT and pulse oximeter. The device continuously records 4 channels: PAT signal, oxyhemoglobin saturation, actigraph determined sleep-wake states, and PR derived from the PAT signal.[297] All recorded signals were stored at a sample rate of 100 Hz on a removable flash disk which could be downloaded and analyzed by commercial software (zzzPAT, Itamar, Israel).

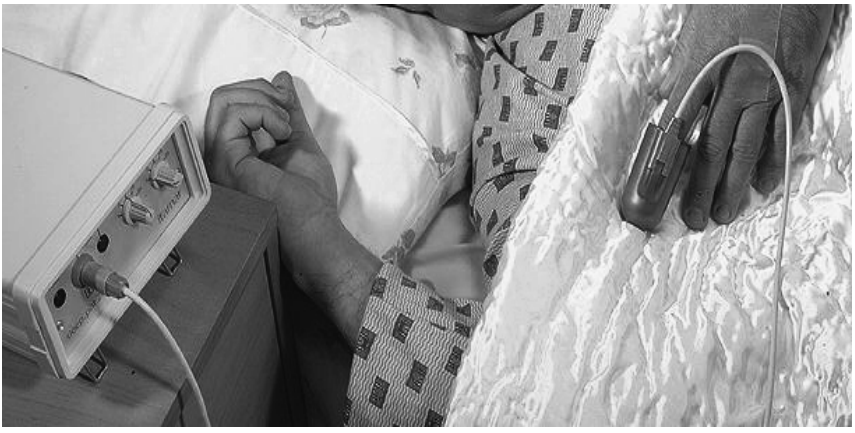

Figure 10. The Sleep PAT 200 device (photo courtesy of Itamar, with permission)

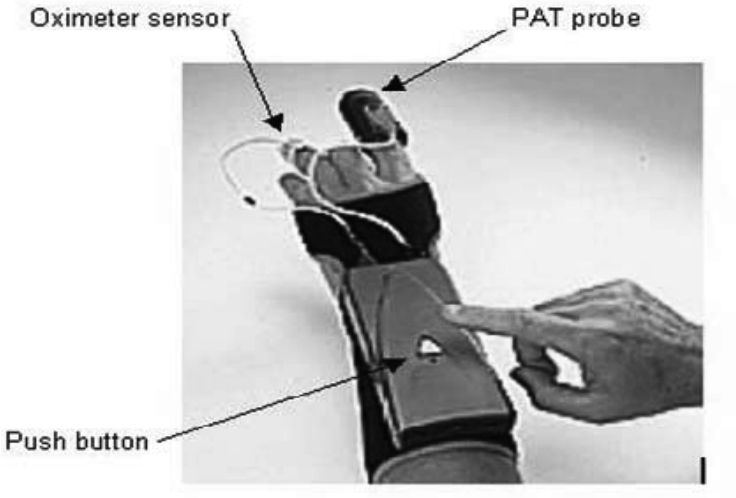

Figure 11. The WP100 device, adapted from Bar et al. Chest 2003.[297]

3.9.3 zzzPAT program

The zzzPAT program was used to automatically analyze sleep/wake time and SDB events in study III. In brief, the sleep time detection window is determined by total recording time minus the wake time and time of invalid signals.[322] The total recording time was defined as follows: (1) start time of the study defined as the time when the device was switched on using the "on button"; (2) end time of the study determined by the "truncation algorithm"—identification of the disappearance of the pulse wave (the probe had been removed); (3) total recording time was the time period between "start time" and "end time".

Specific algorithms were used to automatically detect different types of respiratory events. The WP100 indices (ODI, AHI, and RDI) were calculated as number of events per hour of sleep based on the detected sleep time. All oxygen desaturation events reaching 4% or more during the sleep periods were used for calculation of the ODI. The algorithms used for AHI and RDI calculation were mainly based on 2 components: the oxygen saturation data plus an indication of autonomic activation from the PAT signal. Events for AHI and RDI calculation were defined as follows: (1) any oxygen desaturation event of 3% or more was counted into both the AHI and RDI; (2) a respiratory event detected from the PAT signal was based on a PAT attenuation that was coupled with PR acceleration. There were no fixed thresholds for definition of PAT attenuation and PR acceleration; they were specifically defined per each segment of the study on the basis of the local ODI level. The local ODI analysis was performed by a sliding window of 5-minute in a first-run analysis. Subsequently, in a second-run analysis, the algorithm detected events when the PAT and PR thresholds were modified based on the local ODI. The AHI and RDI algorithms used specific thresholds related to the PAT attenuation and PR acceleration. Additional input to this algorithm was provided by the motion detector as an indication of a movement arousal. Since the algorithm associated the autonomic activations to oxygen desaturations on the time axis, detected events could be considered as respiratory arousals.

3.9.4 PSG-WP100 synchronization

Epoch-by-epoch comparison was performed to validate WP100 device with ambulatory PSG in study III. The WP100 device was connected during PSG electrode application. The PSG and the WP100 system were synchronized using a continuous synchronization signal generated by the WP100 and recorded on both devices. This signal was later processed by a specifically designed algorithm to achieve minimal synchronization error. The error was in the order

of that generated by computer internal clock differences. This error was identified and taken into account during the comparison process.[322]

3.9.5 PAT analyses in study I and II

The PAT analyses in study I and II were focused on apneic event associated changes. In study I, apnea/hypopnea events in NREM sleep during each experimental step were first classified. PAT signals associated with the events were isolated and exported via the PSG program (Somnologica 3.0, Embla, USA). Self-developed software was applied for PAT amplitude analysis. PWA assessed from the PAT recording was determined during and for 21 seconds following each event. The change in PWA across the apnea/hypopnea event including the post-apnea/hypopnea period was calculated separately for each event and expressed as the PAT ratio. This was defined as the mean of the three smallest consecutive PAT pulse amplitudes in the 21-second post-apnea/hypopnea period divided by the mean of the three largest consecutive PAT amplitudes during the apnea/hypopnea itself and multiplied by 100. Vasoconstriction at the post apnea phase thereby could be reflected by lower PAT ratio (less than 100%). In study II, all the apnea/hypopnea events during sleep were exported and the associated PAT amplitude changes were analyzed using the same program.

3.9.6 PAT amplitude analysis in study IV

The PAT attenuations from overnight sleep recordings were analyzed irrespective sleep stages and respiratory events in study IV. The PAT signals derived from WP100 were studied using custom software developed in the laboratory. The raw PAT signal was first bandpass filtered to remove LF drift and HF noise. After rescaling for normalization, PAT amplitude was detected as the difference between a local peak and the attenuation "trough" that preceded it. Finally, the detection of attenuation events was made using a robust peak detection algorithm according to heuristic criteria (slope, amplitude and attenuation period). Attenuations were required to last at least 3 s but less than 30 s and expressed as percentage change.

3.10 CV risk classification in study V

Overall CV risk assessment was performed using the well established European Society of Hypertension/European Society of Cardiology (ESH/ESC) risk factor matrix[323] in study V (Figure 12a, 12b). A modified version of the Basic Nordic

Sleep Questionnaire covering the occurrence of all major CV diseases was completed by the subjects. In addition, BMI and office BP were assessed according to the World Health Organization standard.[317] The presence of CV risk factors and/or concomitant CV disease was further determined by a physician during a clinical interview and physical examination. Finally, the patient's comprehensive hospital medical record was reviewed for diagnoses of CV disease. Drug treatments were assessed and coded according to the anatomical therapeutic chemical classification system. This information was used to determine CV risk scores based on the ESH/ESC risk factor matrix ranging from "average risk" (CV risk category 1), "low added risk" (CV risk category 2), "moderate added risk" (CV risk category 3), "high added risk" (CV risk category 4) and "very high added risk" (CV risk category 5). In study V, average to moderate CV risk (CV risk category 1, 2 and 3) was allocated to a low CV risk group and compared with a high CV risk group (CV risk category 4 and 5).

	Blood pressure (mmHg)				
Other risk factors and disease history	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 SBP 140–159 or DBP 90–99	Grade 2 SBP 160–179 or DBP 100–109	Grade 3 SBP ≥ 180 or DBP ≥ 110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors or TOD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
ACC	High added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

ACC, associated clinical conditions; TOD, target organ damage; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Figure 12a. ESH/ESC risk factor matrix.[323]

Factors influencing prognosis

Risk factors for cardiovascular disease used for stratification	Target organ damage (TOD)	Diabetes mellitus	Associated clinical conditions (ACC)
• Levels of systolic and diastolic BP • Men > 55 years • Women > 65 years • Smoking • Dyslipidaemia (total cholesterol >6.5 mmol/l, >250 mg/dl*, or LDL-cholesterol > 4.0 mmol/l, >155 mg/dl*, or HDL-cholesterol M < 1.0, W < 1.2 mmol/l, M < 40, W < 48 mg/dl) • Family history of premature cardiovascular disease (at age < 55 years M, < 65 years W) • Abdominal obesity (abdominal circumference M ≥ 102 cm, W ≥ 88 cm) • C-reactive protein ≥1 mg/dl	• Left ventricular hypertrophy (electrocardiogram: Sokolow–Lyons >38 mm; Cornell >2440 mm*ms; echocardiogram: LVMI M ≥ 125, W ≥ 110 g/m²) • Ultrasound evidence of arterial wall thickening (carotid IMT ≥ 0.9 mm) or atherosclerotic plaque • Slight increase in serum creatinine (M 115–133, W 107 – 124 µmol/l; M 1.3–1.5, W 1.2–1.4 mg/dl) • Microalbuminuria (30–300 mg/24 h; albumin–creatinine ratio M ≥ 22, W ≥31 mg/g; M ≥ 2.5, W ≥ 3.5 mg/mmol)	• Fasting plasma glucose 7.0 mmol/l (126 mg/dl) • Postprandial plasma glucose > 11.0 mmol/l (198 mg/dl)	• Cerebrovascular disease: ischaemic stroke; cerebral haemorrhage; transient ischaemic attack • Heart disease: myocardial infarction; angina; coronary revascularization; congestive heart failure • Renal disease: diabetic nephropathy; renal impairment (serum creatinine M > 133, W >124 µmol/l; M >1.5, W > 1.4 mg/dl) proteinuria (>300 mg/24 h) • Peripheral vascular disease • Advanced retinopathy; haemorrhages or exudates, papilloedema

M, men; W, women; LDL, low-density lipoprotein; HDL, high-density lipoprotein; LVMI, left ventricular mass index; IMT, intima-media thickness. *Lower levels of total and LDL-cholesterol are known to delineate increased risk, but they were not used in the stratification

Figure 12b. ESH/ESC risk factor matrix.[323]

3.11 Pulse oximetry signal analysis in study V

In study V, a novel finger photoplethysmographic pulse oximeter sensor (ChipOx, MCC, Germany) was developed to quantify the pulse wave signal. These pulse signals were recorded on a separate analog data logger (Physiologg data logger, Institute for Aviation and Space Research, University of Cologne, Germany) in parallel with PSG recordings. During polygraphy recordings, the signals were directly recorded by the inbuilt oximetry module. Recordings with minimum 3 hours artifact free oximeter signal were included in the ASI analysis.

3.11.1 Physiological parameters derived from finger pulse oximetry

The photoplethysmographic pulse wave signal was first collected with a sampling frequency of 50 Hz and filtered using a 2nd order Butterworth lowpass filter with cut-off frequency of 10 Hz to remove noise. Five physiological parameters including PWA attenuation, pulse propagation time (PPT), respiration related pulse oscillation (RRPO), pulse rate acceleration and oxygen desaturation were derived from the beat-to-beat signal without averaging and saved at a sampling rate of 5 Hz. Time and frequency information from PWA attenuation, pulse rate acceleration and oxygen desaturation were extracted using a Matching Pursuit Algorithm,[324] which is an established, wavelet-related signal analysis method. Indices of PWA attenuation, pulse rate acceleration and oxygen desaturation were calculated from the total recording time. These 3 indices and the whole night means of PPT and RRPO were applied for the development of the CV risk classification algorithm.

3.11.1.1 Pulse wave attenuation index (PWA-I)

PWA attenuation was defined as a decrease of 30% or less in PWA compared to baseline (a moving median value of 20 samples surrounding the observed sample). The number of the attenuations per hour was calculated as PWA-I.

3.11.1.2 Mean pulse propagation time

The PPT was defined as the time interval between the systolic and dicrotic notch of the pulse waveform. The mean PPT of the complete recording time was reported.

3.11.1.3 Mean respiration related pulse oscillation

The RRPO was calculated by measuring the breathing associated oscillation (respiratory sinus arrhythmia in the frequency band between 0.15–0.4 Hz) from the PR signal in the time domain. A mean value of the complete recording was reported.

3.11.1.4 Pulse rate acceleration index (PR-I)

The pulse rate acceleration was defined as a ≥10% PR increase from baseline (a moving median value of 20 samples surrounding the observed sample). The number of the accelerations per hour was calculated as PR-I.

3.11.1.5 Hypoxia index (SpO_2-I)

This oxygen desaturation event was defined as ≥2% drop of saturation of each sample compared to a 90-s time window of the upcoming oxygen saturation signal (no baseline averaging). The number of desaturation events per hour was calculated as SpO_2-I.

3.11.2 Autonomic state indicator algorithm

For the identification of high risk patients, a neuro-fuzzy system[325] was constructed and trained using a randomly selected subset of the patient recordings (n=99). A 3-layer fuzzy perceptron with one hidden layer was used. The perceptron contained five input nodes from the five ASI components, a four node hidden layer and one output layer which determined the probability that the input vector belonged to a high risk patient. For the fuzzification process, trapezoid membership functions were used. The fulfillment grade of each data vector to belong to a high risk patient was computed by using min/max inference and was scaled to the output range of [0;1]. The final classification was done by testing the output value of the neuro-fuzzy system with a threshold of 0.5 in order to classify high risk patients. The ASI algorithm was further tested in a validation set of patients (n=49).

3.12 Statistical analysis

Analyses were performed using statistical program SPSS (SPSS, USA) and R software language with the Design library. Continuous variables were expressed

as means ± SD or mean ± SE. Two tailed P values <0.05 were considered statistically significant.

In study I, the vascular effects at each dose level of phentolamine infusion on PAT ratio were analyzed using linear mixed effects regression models with paired individual intervention contrasts with the baseline. The mean of MAP and PR at baseline and following interventions were compared within each subject using paired sample t-test.

In study II, continuous variables were compared between drugs using univariate ANOVA. Linear mixed effects regression models were used to identify the contributions of medication, apnea desaturation and sleep stage to the PAT ratio.

In study III, Pearson correlation tests were used to test the AHI, RDI, and ODI correlation between the WP100 and PSG. Bland-Altman plots were used to test the repeatability of AHI, RDI, ODI between WP100 and PSG. ROC analysis was performed to validate the WP100 diagnostic capability. Thresholds of PSG AHI >10, 15, and 20 and RDI >10, 15, and 20 were used as different cut-off points for OSA diagnosis. Area under the curve (AUC) was calculated. The agreement between WP100 automatic sleep-time analysis and PSG-scored total sleep time was compared.

In study IV, statistical analyses were performed with generalized least squares regression models using the R language[326] and NLME library to identify the association between median PAT attenuation (PWA.att) and office systolic/diastolic BP adjusted for gender, age, BMI, antihypertensive medications, and PSG indices.

In study V, a multivariate proportional odds logistic regression model was used to examine the relationships between the five ASI components and the ESH/ESC classified CV risk. Agreement between the ASI and the ESH/ESC risk strata (high risk vs. low risk) was indexed using Cohen's Kappa. Sensitivity and specificity of the ASI algorithm was evaluated by applying a diagnostic cut off level between the high and low risk groups.

MAIN RESULTS

4.1 Study I: Experimental intervention

Eight male patients with severe OSA were enrolled in the study (age 53±4 yrs, BMI 31±2 kg/m^2, BP 137±7 / 80±5 mmHg, HR 68±3 bpm, AHI 79±6 events/h). The pulsatile volume signal assessed from PAT displayed periodical attenuation after spontaneous apnea/hypopnea events coinciding with arousals. Altogether 1036 obstructive apnea/hypopnea events during NREM sleep (mainly sleep stage 1 and 2) were analyzed in the study (baseline n=350, phentolamine 0.066, 0.2, 2 and 5µg, n=202, 190, 202, 92, respectively). The mean PAT ratio at baseline was 33.9±3.8% suggesting a considerable attenuation of PAT amplitude in the post-event phase. A dose-dependent increase in PAT ratio with a threshold of 0.066µg was demonstrated during the cumulative dose administration of phentolamine. The PAT ratio increased by 11.2±1.7%, 24.4±2.1%, and 30.9±4.1% compared with baseline after the three higher concentration steps of phentolamine (0.2, 2 and 5µg $P<0.001$, respectively) (Figure 13). A typical recording demonstrating the PAT amplitude changes during different experimental steps is shown in Figure 14.

Systemic hemodynamic was generally stable during the infusion protocol and comparable to baseline. MAP decreased 5.3±0.3 mmHg ($P=0.04$) during the apnea event at the 5µg concentration level of phentolamine. The post-event PR was lower 2.7±1.0 bpm ($P=0.033$) after phentolamine 2µg infusion compared with baseline. The mean event length compared with baseline was unchanged during all the interventions. There were only small and inconsistent differences in oxygen desaturation between the baseline and phentolamine infusions mainly due to spontaneous variation.

4.2 Study II: Pharmacological intervention

Sixteen male hypertensive OSA patients were recruited in the study (age 55±7 yrs, BMI 30.1±3.8 kg/m^2, BP 165±14 / 98±8 mmHg, HR 76±11 bpm). Two patients, one on DO and one on EN, did not complete the study due to sweating and palpitations. The mean reductions in office BP after treatment were systolic BP-4.1±11.1 and -12.6±15.9 mmHg, diastolic BP -5.1±7.5 and -8.9±6.5 mmHg, for DO and EN respectively. There were no statistically significant differences

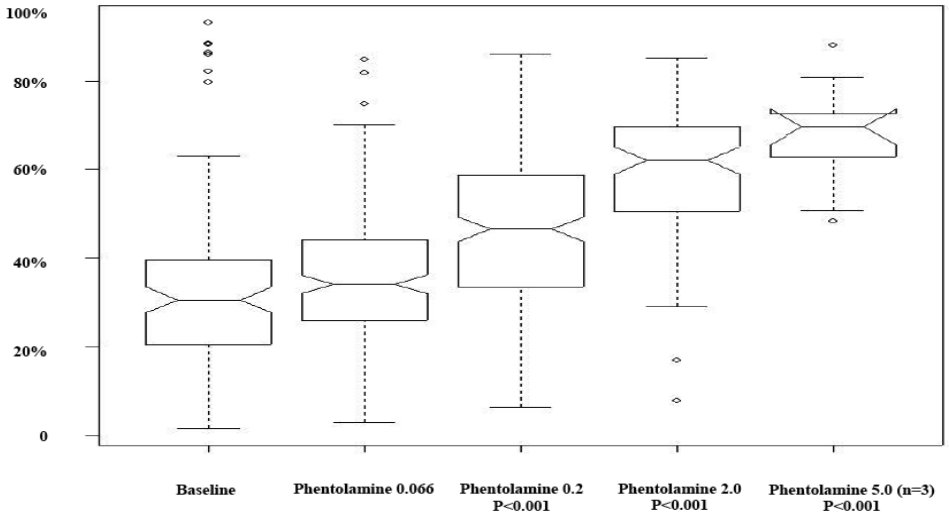

Figure 13. PAT ratio at baseline and phentolamine infusion. The upper and lower limits of boxes depict the 25- and 75-percentiles of the data, respectively. The width of the notche in the box represents the 95% confidence intervals for the median.

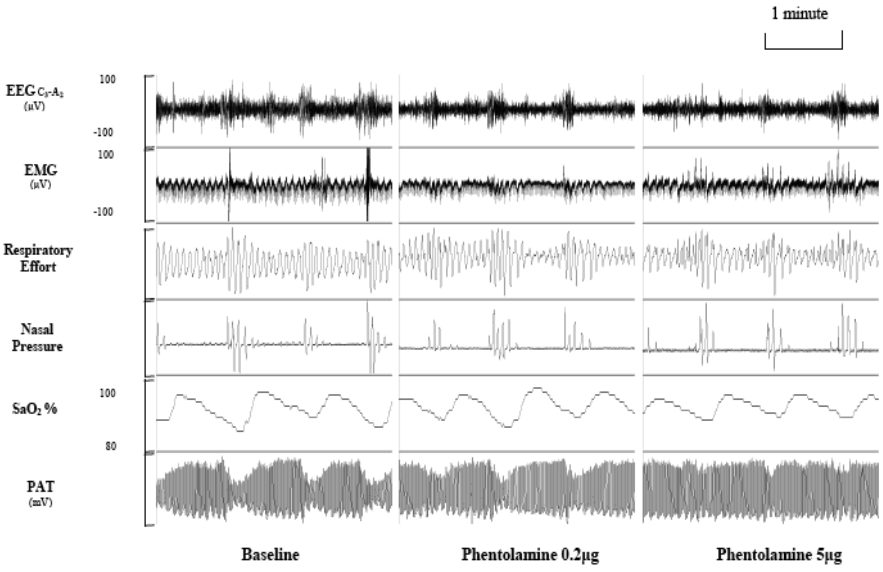

Figure 14. An example of PAT amplitude change during apenic events at baseline, phentolamine 0.2 and 5.0 μg/min/100ml forearm volume infusion.

between the two treatments with regard to the 24-hour BP profile and office BP. Nighttime beat-to-beat finger BP was significantly lower in patients receiving EN treatment (systolic BP 129±13 vs.119±23 mmHg, P = 0.02; diastolic BP 81±12 vs. 74±14 mmHg, P=0.04, for DO and EN respectively). The AHI, ODI, ARI and mean oxygen desaturation did not differ systematically between the two treatments (Table 7). The mean PAT ratio was greater under DO treatment compared with EN treatment (40.3±18.9% vs. 35.0±20.6%, P<0.001). Univariate analysis using linear mixed effects regression model suggested the degree of vasoconstriction (PAT ratio) was related to the degree of hypoxia to an extent where each 1% increase in oxygen desaturation was associated with a

Table 7. Hemodynamic and sleep parameters at the end of doxazosin and enalapril treatments (mean ± SD)

	DO	**EN**	**P value**
24-h BP monitoring			
24-h systolic BP (mmHg)	140±12	138±17	0.69
24-h distolic BP (mmHg)	86±9	85±11	0.85
24-h HR (bpm)	80±8	78±10	0.58
Daytime systolic BP (mmHg)	144±13	142±17	0.67
Daytime diastolic BP (mmHg)	88±9	88±12	0.97
Datime HR (bpm)	82±10	81±10	0.62
Nighttime systolic BP (mmHg)	124±15	126±15	0.85
Nighttime diastolic BP (mmHg)	74±10	75±9	0.91
Nighttime HR (bpm)	69±7	68±9	0.67
Office BP			
Office systolic BP (mmHg)	160±18	149±21	0.15
Office diastolic BP (mmHg)	95±9	93±9	0.50
Office HR (bpm)	86±10	85±10	0.67
Beat-to-beat BP monitoring			
Systolic BP (mmHg)	129±13	119±23	**0.02**
Diastolic BP (mmHg)	81±12	74±14	**0.04**
PSG monitoring			
Total sleep time (min)	310±58	321±63	0.61
REM sleep time (min)	42±18	47±34	0.61
Apnea hypopnea index (events/hour)	43±22	41±21	0.84
NREM apnea hypopnea index (events/hour)	43±23	40±22	0.78
REM apnea hypopnea index (events/hour)	45±25	48±26	0.80
Oxygen desaturation index (events/hour)	36±24	37±22	0.97
Arousal index (events/hour)	45±17	45±18	0.99
ESS score	9±5	9±4	0.83

0.9% decrease of PAT ratio (P<0.001). PAT ratio during sleep apnea events was also associated with sleep stage and was 2.2% lower during REM sleep relative to NREM sleep (P=0.002).

4.3 Study III: Validation of WP100 vs. ambulatory PSG

Of the 106 participants, data from 8 subjects were rejected from the analyses due to WP100 recording failure (7 subjects had no recording or PAT signal, and oximetry failure occurred in 1 subject). Six subjects had oximetry failure in the ambulatory PSG recording, and data from these subjects were excluded from ODI comparison. In one subject, a substantial portion of the oxygen saturation signal in the PSG recording was lost but was retained in the ODI comparison.

The final study population (n=98, 55 men) had a mean age of 60±6.7 years, BMI of 28.0±4.2 kg/m^2, and ESS score of 6.0±3.5. A total of 21 subjects had a known history of hypertension, and 2 subjects had diabetes. The sleep and breathing characteristics from the PSG and the WP100 recordings are shown in Table 8. There was a strong correlation between the AHI, RDI, and ODI assessed by WP100 and PSG (r^2=0.81, 0.77 and 0.85, P<0.001, respectively). The Bland-Altman plot revealed a good agreement between the WP100 and PSG assessment of AHI and RDI (mean difference 1.5±10.2 and -1.2±10.9 events/hr, respectively) (Figure 15a, 15b). The WP100 tended to overscore ODI in this population (mean difference 4.4±6.5 events/hr, P<0.001). ROC curves were constructed for WP100 sensitivity and specificity at different thresholds—PSG AHI and RDI 10, 15 and 20, respectively. The AUCs were 0.93, 0.92, and 0.93 for PSG AHI >10, 15, and 20; 0.88, 0.88, and 0.90 for PSG RDI>10, 15, and 20, P<0.001, respectively.

Table 8. Sleep and breathing characteristics comparing PSG and WP100

	PSG	**WP100**
Total sleep time (hour)	6.5 ± 1.2	6.3 ± 1.3
AHI (events/hour)	25.5 ± 22.9	27.0 ± 18.7
RDI (events/hour)	31.6 ± 22.7	30.4 ± 18.7
ODI (events/hour)	13.3 ± 15.3	17.7 ± 16.7 *

Mean ± SD * P < 0.001

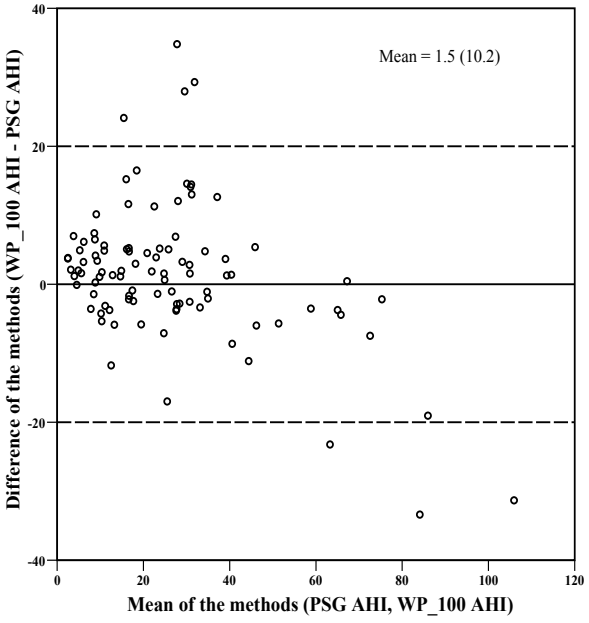

Figure 15a. Bland-Altman plot of AHI comparison

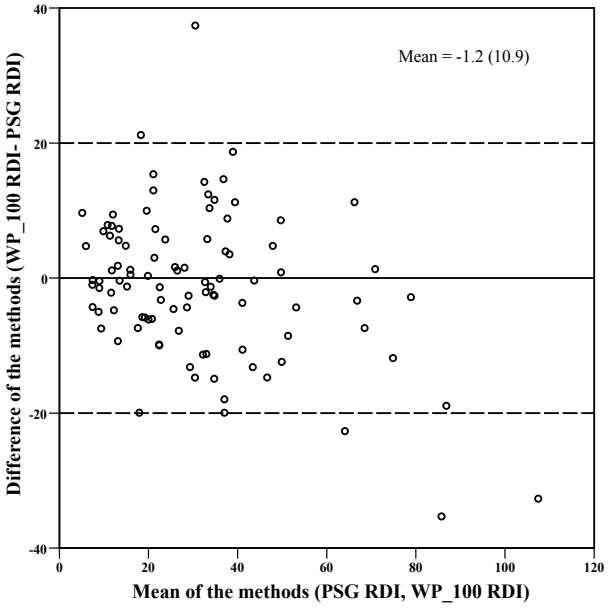

Figure 15b. Bland-Altman plot of RDI comparison

4.4 Study IV: Cross-sectional analysis of PAT attenuation and office BP

A total of 81 subjects (46 men, 35 women) were included in the analysis with a mean age of 60±7 years, BMI of 28.2±4.3 kg/m^2, systolic BP of 137±15 mmHg and diastolic BP of 79±7 mmHg. Fourteen subjects used antihypertensive medication. The mean AHI and ODI of the study population were 25.4±22.6 and 13.8±16.1 events/hour, respectively. The total sleep time of the subjects was 393±62 min. A mean of 1151±237 PAT attenuation events were identified from the overnight PAT recordings and the PWA.att was 20.8±7.5%.

Using multivariate regression analysis, we modeled the relationships between office systolic/diastolic BP and PWA.att using the following predictors: gender, age, BMI, antihypertensive medication, number of attenuation episodes, AHI, ODI and ARI. We found that the association between PWA.att and office BP was independent (i.e., no interaction) of other predictors.

In a reduced univariate model, we found that each 10% increase in PAT attenuation was associated with increases of 5.0 mmHg systolic BP (P=0.02) and 3.0 mmHg diastolic BP (P=0.005). We also found independent relationships between systolic BP / diastolic BP and BMI (P=0.0006/0.001), AHI (P=0.03/0.1) and ODI (P=0.03/0.03). Correlations between selected variables are shown in Table 9.

Table 9. Cross correlation between different parameters and office BP.

	PWA.att	Number of PWA attenuations	AHI	ODI	BMI
Systolic BP	0.26*	-0.13	0.24*	0.24*	0.37*
Diastolic BP	0.31*	-0.17	0.18	0.24*	0.35*
PWA.att		-0.31*	0.51*	0.51*	0.30*
Number of PWA attenuations			-0.11	-0.09	0.00
AHI				0.90*	0.29*
ODI					0.35*

*P< 0.05

4.5 Study V: CV risk assessment based on pulse oximetry derived signals

A total of 148 subjects (98 men, age 50±13 years, BMI 27.6±5.4 kg/m^2) were included in the final analysis. Previously known systemic hypertension and ischemic heart disease were found in 47 and 9 patients, respectively.

4.5.1 Nocturnal pulse wave form and PR variation

Repetitive and/or spontaneous attenuations of PWA were found during the night in all the subjects. The most frequent PWA attenuations were spontaneous and between 10-30% from baseline. More pronounced attenuations of the pulse wave signal (>40% from baseline) and pulse rate accelerations were typically associated with respiratory events, periodic limb movements or body movements. An example of three-minute recording without detectable EEG arousal is shown in Figure 16.

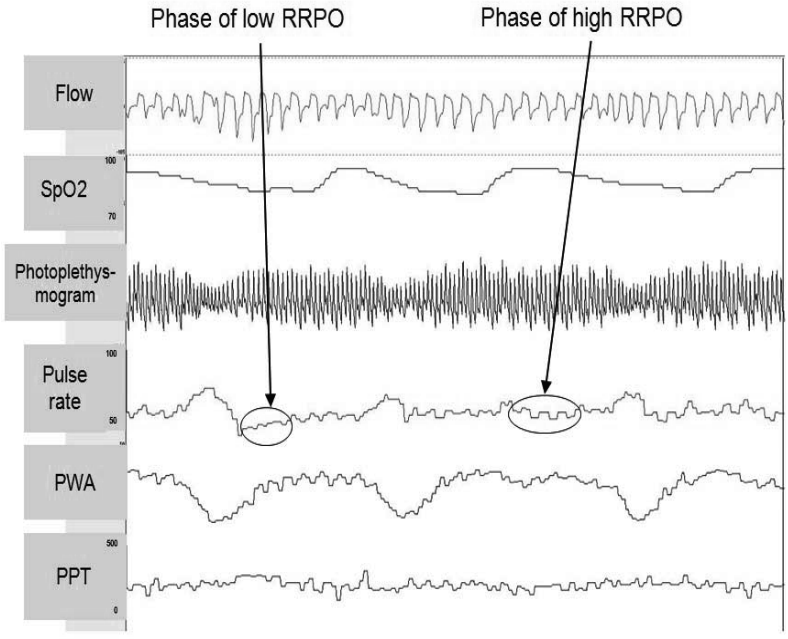

Figure 16. Three-minute recording trace without EEG arousal in NREM sleep.

4.5.2 CV risk and ASI components: multivariate logistic regression

According to ESH/ESC CV risk matrix, 47, 43, 32, 10 and 16 patients were classified as CV risk category 1, 2, 3, 4 and 5, respectively. The relationships between the five ASI parameters and the ESH/ESC CV risk score were examined using multivariate logistic regression models. Individual models of each of the predictors (PWA-I, PPT, RRPO, PR-I and SpO_2-I) accounted for between 60% and 70% of the models discriminatory power (*c* index). The performance of these variables in predicting CV risk was variable but data suggested that each variable provided a strong association with a shift in risk class which was statistically significant for all variables (PPT P<0.0001, RRPO P=0.02, PR-I P=0.01, SpO_2-I P=0.0001, respectively), except PWA-I (P=0.08). Spearman correlation analyses showed that the five ASI variables were interrelated with r^2=0.04 to 0.18. A multivariate model using all five ASI variables was validated using 200 bootstrap replications with backwards stepwise term elimination. Indeed, each of the five variables contributed significantly to the model fit and none could be effectively eliminated. This full model predicted risk class with a discrimination index of 79% ($X^2_{(5)}$ = 59.5, P<0.0001). The individual risk odds are illustrated in Figure 17. Finally, the diagnostic sensitivity and specificity of the computed composite ASI-CV risk score for separation of the ESH/ESC matrix derived CV risk class 1 to 3 (average to moderate risk) from class 4 and 5 (high and very high risk) were determined. The overall agreement between the two risk assessment tools in an analysis including all 148 patients was 81% with a Cohen's Kappa of 0.5 (P<0.001).

4.5.3 Assessment of CV risk by ASI algorithm: External validation

There was no systemic difference in anthropometric data between the training and the validation cohorts (Table 10). Comorbid CV and pulmonary disease were equally prevalent in both groups. Concomitant medications with potential effects on cardiac and vascular reactivity were similar in the training sample and the validation group.

Diagnostic sensitivity and specificity of the neuro-fuzzy-classifier derived ASI-CV risk score was compared with the ESH/ESC matrix derived risk classification using separate training (n=99) and validation (n=49) patient samples. In the training set, 13 out of 16 (sensitivity 81%) patients with high or very high (class 4 and 5) CV risk were correctly identified whereas 70 out of 83 (specificity 84 %) patients with average to moderate (class 1 to 3) CV risk were

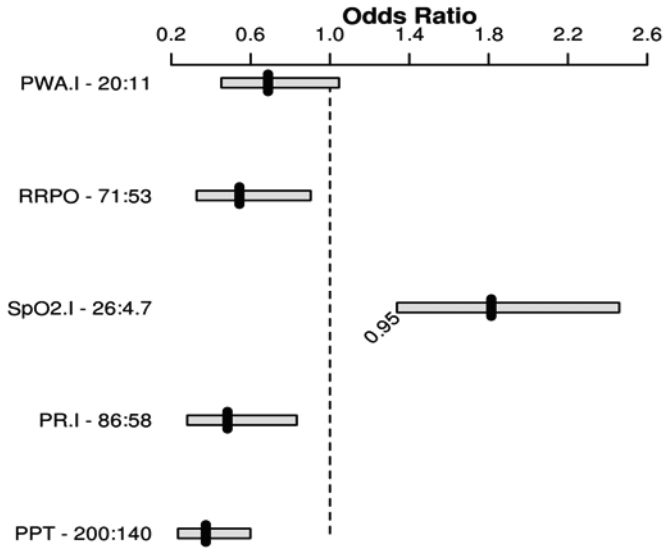

Figure 17. Odds ratios, with 95% confidence limits, for CV risk class progressions over interquartile range spans of each ASI parameter (e.g., PPT 200:140). For example, a subject with a SpO_2-I of 26 exhibits a 1.7 times greater risk of being in a higher CV risk class compared to a subject with a SpO_2-I of 4.7. PWA-I=pulse wave attenuation index; RRPO=respiration related pulse oscillation; SpO_2–I=hypoxia index; PR-I=pulse rate acceleration index; PPT=pulse propagation time.

identified. In the validation set, 8 out of 10 (sensitivity 80%) patients with high or very high CV risk and 30 out of 39 (specificity 77%) patients with average to moderate CV risk were correctly classified. Six out of the 9 patients that were falsely classified as high risk by the ASI algorithm belonged to the ESH/ESC moderate added risk class (CV class 3). Positive and negative predictive values were 0.47 and 0.94, respectively. Concomitant use of medication (ATC codes C01, C03 and C07-10) was recorded in 55 patients (Table 11) and β-blocker treatment was identified as an important factor for classification that was not in line with the ESH/ESC matrix. A ROC curve for the ASI-CV risk score was constructed using a defuzzyfication threshold >0.5 to identify the patients at high CV risk in the validation group. The AUC was 0.84 (Figure 18).

Table 10. Patient characteristics in the training and validation cohorts.

	Training Cohort (n=99)	**Validation Cohort** (n=49)	**P value**
Sex (M/F)	67 / 32	31 / 18	
Age (years)	50 ± 13	52 ± 13	0.39
Smoking (never / current / past)	51 / 13 / 35	20 / 6 / 22	
BMI (kg/m^2)	27.4 ± 5.5	27.9 ± 5.3	0.66
Office systolic BP (mmHg)	134.4 ± 21.1	133.5 ± 18.1	0.79
Office diastolic BP (mmHg)	79.9 ± 11.1	78.5 ± 10.0	0.48
Pulse rate (bpm)	66.7 ± 14.0	65.6 ± 11.1	0.65
ESS Score	10.8 ± 6.0	10.0 ± 6.0	0.40
AHI (n/hour)	20.0 ± 26.1	19.7 ± 25.5	0.83
ODI (n/hour)	14.1 ± 23.1	16.0 ± 23.5	0.75
Number of patients with AHI >15/h	39 (39.4%)	17 (34.7%)	0.71

Table 11. Prevalence of comorbidity and concomitant CV medication use within ATC code groups C01-C10. Note that multiple conditions may apply in a single patient.

Comorbidity or drug usage (subgroup and ATC code)	**Training Cohort** (n=99)	**Validation Cohort** (n=49)	**P value**
Systemic hypertension	30%	35%	0.54
Coronary artery disease	6%	8%	0.68
Stroke	4%	6%	0.66
Congestive heart failure	3%	6%	0.25
Diabetes mellitus	11%	18%	0.19
Chronic obstructive pulmonary disease	10 %	8%	0.97
C01 – Nitrates	5%	2%	0.73
C03 - Diuretics	10%	18%	0.24
C07 – β-blocking agents	18%	26%	0.24
C08 - Calcium channel blockers	5%	6%	0.79
C09 – Renin-Angiotensin modulators	15%	12%	0.64
C10 - Lipid lowering drugs	15%	14%	0.89

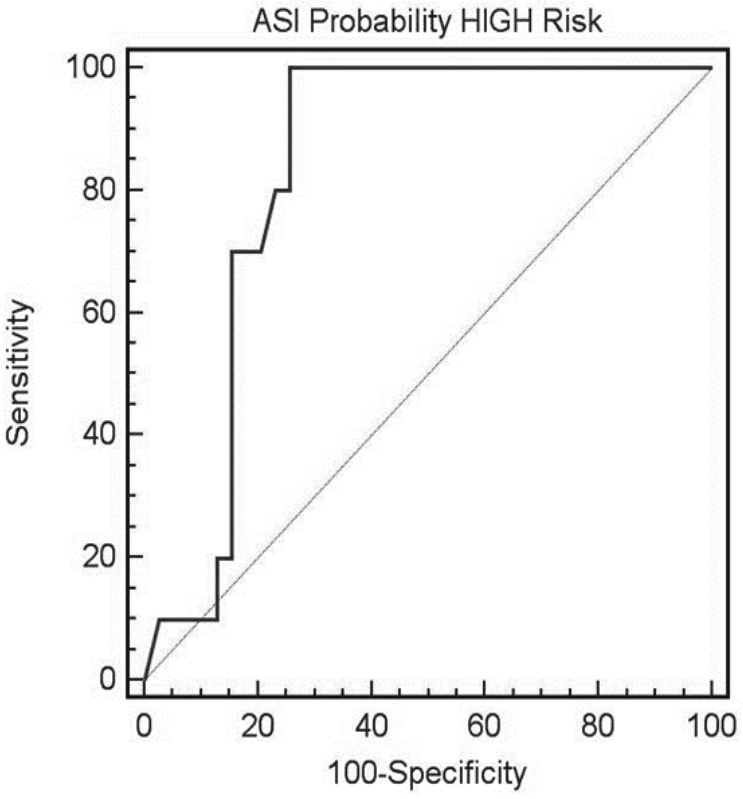

Figure 18. A ROC curve showing the sensitivity and specificity of the ASI-CV risk score for correct classification of high CV risk according to ESH/ESC matrix in the validation set (n=49), AUC=0.84.

DISCUSSION

5.1 Physiological mechanism of PAT attenuation

5.1.1 Finger blood flow and PAT ratio

Cutaneous blood flow fluctuates in response to ambient temperature, diurnal rhythm, and varies between individuals.[290,291,294,327] Although the magnitude of these changes cannot be strictly quantified, the recorded photoplethysmographic PAT signal bears a direct relationship with finger blood perfusion. The increased light attenuation that occurs with each heartbeat is associated with a pulsatile increase of blood volume in the finger vascular bed.

The PAT ratio calculation applied in study I and II was constructed to provide a measure of the relative change of digital blood flow occurring during each apnea/hypopnea event. It should be emphasized that a change in the PAT ratio could have occurred as a consequence of a change in PAT amplitude during the post-event phase, an alteration of the amplitude during the event or a combination of the two. However, the increase in the PAT amplitude during the post-event period provides the main contribution to the increase in PAT ratio in the interventional studies as the amplitude changed only marginally during the event.

There was a time delay in the order of 3-7 s from the initiation of electrophysiological arousal to the nadir of the PAT amplitude most likely reflecting latency caused by a delay at the vascular target tissue level. A 21-second time window during the post event period was applied in order to cover all the amplitude attenuation related to the event.

5.1.2 Effect of phentolamine on PAT ratio

In study I, phentolamine reversed the PAT attenuation during the post apnea period in a dose-dependent manner suggesting an α-receptor mediated vasoconstrictory mechanism. Phentolamine has previously been demonstrated to increase finger blood flow during body cooling while nitroprusside, a direct smooth muscle dilator, was ineffective.[328] Thus, in this infusion protocol, it is likely that phentolamine induced vasodilation by its α-receptor antagonistic properties rather than by a nonspecific vasodilator response.

The attenuation of the constrictory response was incomplete even at the highest dose level of phentolamine studied. The reason for this finding is not fully understood but may be explained by tonic skin blood flow fluctuations in the finger vascular bed. The slight reduction of arterial BP during peak dosing of phentolamine can also cause reflex vasoconstriction that affects the PAT ratio. However, the α-adrenergic receptor blockade effect of phentolamine was seen already at lower dose levels not affecting BP.

5.1.3 Effect of doxazosin on PAT ratio

In study II, DO (a peripheral α-receptor inhibitor) treatment resulted in a less pronounced apnea related digital vascular constriction response compared to EN. The finding further supports the notion that sympathetic activation in the finger vascular bed during the post apnea period (reflected by the PAT ratio) is α-receptor mediated. The fact that EN has little effect on skin vascular blood flow[329] makes it plausible that the PAT ratio after EN treatment is similar to the untreated baseline condition. This circumstance would enable us to overcome the limitation that the baseline measurements were not performed in the study.

The magnitude of the PAT ratio change was smaller during DO treatment compared with phentolamine infusion. The difference may be explained by a lower concentration of the α-receptor antagonist in the local vascular bed. Another possible explanation could be that the BP reduction induced by DO caused an increase of sympathetic outflow and thereby masked the change of the PAT ratio.[330]

Although digital vasoconstriction associated with OSA is mainly caused by arousal, severe upper airway obstruction without EEG arousal can lead to PAT attenuation.[331] In study II, we found a small, but significant association between the PAT ratio and the change of oxygen saturation level suggesting that the severity of apnea, as reflected by oxygen desaturation, is linked to digital vascular constriction. The study also demonstrated that REM sleep was associated with more pronounced apnea-induced PAT attenuation compared with NREM sleep. This finding is not unexpected considering that REM sleep is traditionally associated with more severe apnea episodes and increased sympathetic activity compared with NREM sleep.

5.2 Application of PAT in clinical sleep medicine

Following the initial proposal of PAT attenuation as a novel physiological marker of OSA in 1999,[296] there have been several studies that explore the

clinical applications of the technique in sleep medicine. A portable PAT device has been introduced and different PAT analysis algorithms have been constructed for evaluation of SDB and sleep.

5.2.1 PAT attenuation during OSA events

The PAT signal was found to periodically attenuate in association with spontaneous apneic events coinciding with arousals in study I. This finding is line with an early study showing transient periods of PAT attenuation and increased HR to be associated with apnea/hypopnea events during sleep.[296] Using a technique to manipulate the degree of upper airway obstruction, O'Donnell et al.[331] further demonstrated that even in the absence of EEG arousal, PAT attenuation could be triggered by brief airway obstruction with small oxygen desaturation. However, an EEG arousal from the apneic event appeared to lead to more pronounced PAT amplitude reduction. It was concluded that the change of PAT in response to upper airway obstruction is potentiated by concomitant arousal.

5.2.2 PAT and arousal detection

Arousals from sleep are associated with sympathetic activation. As digital vasoconstriction (PAT attenuation) is an α-receptor mediated sympathetic activation phenomenon, it follows that evaluation of PAT attenuations may provide a useful tool to detect episodes of autonomic arousals during sleep. This possibility was explored by Pillar and coworkers using both a fixed in-lab device[332] and a portable device[333]. An autonomic arousal event defined as ≥50% PAT attenuation or ≥30% PAT attenuation plus a 10% PR increase, correlated closely (r^2=0.67) with PSG scored EEG arousal.[332] The arousal index obtained by attended PSG was accurately reflected by an autonomic arousal index derived from WP100 recording (using actigraphy to detect sleep time).[333] It should be noted that other conditions, such as periodic limb movements, can cause autonomic arousal without simultaneous cortical activation.[332]

5.2.3 A portable PAT device for AHI detection and OSA diagnosis

The WP100 is a portable PAT device designed for OSA diagnosis. Several studies beside ours have demonstrated that WP100 is a reliable tool for OSA detection both in the sleep lab[297,334-336] and in the home environment (study III). The device uses a novel actigraphy algorithm for sleep-wake assessment.[322] The indices derived from the WP100 are calculated based on an automatically

scored “sleep time”. The respiratory and arousal events detected by the WP100 are based on PAT attenuation, PR increase, oxygen desaturation and movement detected by actigraphy. In study III, the threshold for PAT attenuation and PR increase to detect respiratory events were based on aspects of local ODI level. This approach may explain why the WP100 device tends to overestimate apnea/hypopnea events in the normal to mild range and to underscore AHI in more severe cases.[334] For instance, flow limitation accompanied by subtle EEG changes not fulfilling traditional arousal criteria may cause sympathetic activation which can be detected by the WP100. Multiple apneic events occurring during a short time period can lead to insufficient time for the PAT signal to return to the baseline. In spite of these potential limitations, the WP100 derived AHI and RDI were closely correlated with PSG scored indices in study III (r^2=0.81 and 0.77, respectively).

When the AHI ≥10 and RDI ≥20 thresholds were applied as a diagnostic cut-off for OSA, the area under the ROC curves reflecting the diagnostic capability were 0.93 and 0.90 respectively in study III. These findings were similar to those reported in previous studies investigating the WP100 in sleep laboratory cohorts.[297,334,336] Collectively, these findings suggest that the WP100 may be used for laboratory and ambulatory diagnostic studies of OSA with reasonable accuracy.

5.2.4 A portable PAT device and OSA treatment

Portable monitoring plus auto-CPAP titration can cost-effectively be used for diagnostic work-up and monitoring of treatment in patients with high pre-test-probability of OSA. A study using the WP100 device and auto CPAP pressure titration reported a similar CPAP adherence and clinical outcome as that obtained by conventional PSG and manual CPAP titration.[337] Moreover, the WP100 has been applied to quantify residual respiratory sleep disturbances in OSA patients receiving treatment with CPAP[338] or oral device[339]. Thus, the PAT device has been demonstrated to be a useful tool for follow-up assessment of treatment efficacy in patients with OSA.

5.2.5 PAT and sleep staging

REM sleep is associated with a higher sympathetic activity compared with NREM sleep.[12] PAT, as a measure of sympathetic traffic at the level of the peripheral vascular bed, suggests that REM sleep is associated with a considerable peripheral vasoconstriction.[340] Moreover, the regulation of PAT during REM sleep behaves as a fractal signal.[341] An automatic REM sleep

detection algorithm based on a combination of the PAT signal and actigraphy was therefore developed for the WP100 device.[342] Subsequently, features from two time series of PAT amplitude and inter-pulse periods were used to differentiate deep sleep from light sleep during the NREM sleep period.[343] These sleep staging algorithms were further validated and showed good agreement in a multi-center study (Hedner at al. submission). In 38 normal subjects and 189 patients with suspected OSA, the overall agreement for detection of light/deep and REM sleep were 89±6% and 89±5%, respectively.

5.2.6 PAT and Cheyne-Stokes breathing

CSB is a condition that includes cyclic oscillation of breathing amplitude along with periodical fluctuation of sympathetic nerve activity.[344] A study of 10 heart failure patients with CSB demonstrated that oscillations of the PAT amplitude accompanied CSB during both wakefulness and sleep.[345] The relative attenuation of the PAT amplitude was lower during wake period compared with sleep and the maximum attenuation lagged the start of the crescendo breathing phase by 3-8 s.

5.2.7 PAT and arousal response in children

EEG arousal in children is associated with sympathetic activation reflected by PAT attenuation.[346] However, PAT signal is a highly sensitive but less specific tool in this context.[312,346] In fact, a substantial proportion of autonomic activation defined by PAT were found to occur in children without visually recognizable EEG changes. Whether these attenuations represent normal fluctuations of the autonomic sympathetic nervous system activity in children or reflect subtle sleep disruption that failed to be detected by traditional EEG scoring remains unclear. Nevertheless, PAT seems to provide a useful alternative for improved arousal recognition in children, particularly in the light of that the method may be applied for ambulatory sleep monitoring.

5.2.8 Nocturnal PAT attenuation and daytime BP

In study IV, we found that the magnitude of nocturnal PAT attenuations reflects daytime BP in the general population independent of AHI, ODI, ARI and BMI. This finding implies that vascular or autonomic phenomena recorded during the sleep period provide a marker for vascular disease. Sleep is a condition that enables studies of autonomic regulation with minimum influence from external stimuli. Assuming that the PAT attenuations assessed during a nocturnal recording reflect the overall autonomic nerve system activity during sleep, our

findings suggest that increased sympathetic activity during the night, at least episodic, is associated with elevated office BP during the daytime.[347]

Altered sympathetic nerve activity has been linked to several pathophysiological conditions including hypertension,[348] type 2 diabetes,[349] hyperlipidemia,[350] obesity,[351] myocardial infarction[352] and stroke[353]. Increased MSNA has been reported during both sleep[80] and daytime wakefulness[123] in patients with OSA and is considered as an important underlying pathophysiological mechanism for the development of vascular disease. OSA patients also appear to exhibit an increased variability in nocturnal BP and a blunting of the sleep-related BP fall (non-dipper status).[354] Non-dipping may comprise an elevated risk of end-organ injury as well as fatal CV events.[355] Animal experiment on spontaneously hypertensive rats revealed an elevated peripheral sympathetic outflow during sleep but not during wake periods compared with normotensive controls.[356] Hence, a modified autonomic function during sleep may be an important mechanism in the pathophysiology of hypertension and other forms of CV disease.

Traditional indices derived from PSG recordings are used to quantify the severity of SDB, but have a limited value for the prediction of CV morbidity.[192] A possible explanation could be that the development of CV disease in OSA is a multifactorial process that involves a diverse range of mechanisms. Indices such as the AHI, ODI and ARI, may not be sufficient for detection of important underlying pathogenic mechanisms. The findings in study IV demonstrated that the median level of nocturnal PAT attenuation was more strongly associated with daytime office BP than these indices. Thus, a global parameter such as the surrogate measure of sympathetic activation provided by PAT may reflect complex processes in the development of hypertension and potentially other forms of vascular disease. The signal may therefore be useful for identification of subjects with high risk for CV disease.

As expected, there was an association between BMI and office BP in study IV. BMI is also known to be a major determinant of resting MSNA in healthy subjects.[351] Local sympathetic neuronal responsiveness in the forearm vasculature was positively correlated with BMI.[357] It is possible that the sympathetic nervous system response in the digital vascular bed is modified in obese subjects and the vascular reactivity reflected by PAT signal mirrors such changes. However, the lack of a direct interrelation between the PWA.att and BMI in the study makes this explanation is less likely.

5.2.9 Summary

The PAT signal, reflecting the α-receptor medicated sympathetic activity at the finger vascular bed, can be used to detect obstructive apnea/hypopnea events, CSB and spontaneous arousals during sleep. PAT, together with a simultaneous pulse oximetric signal, PR and an embedded actigraphy, enables a reliable detection of SDB events during sleep, autonomic arousals from sleep, sleep/wake status, REM and light/deep sleep. Episodic PAT attenuation, as a measure of nocturnal increased sympathetic activity, may be used as a novel tool to study CV physiology and morbidity.

5.3 Simultaneous home PSG for portable monitoring device validation

PM devices are mainly intended for unattended sleep study in the patient's home. However, most validation studies of PM devices have been performed in the sleep laboratory setting. In study III, we applied a new validation approach by comparing simultaneous and synchronized PSG and WP100 recordings obtained in the home environment. Although PSG obtained by ambulatory recording has been found to correlate closely with data obtained by PSG in the attended laboratory setting in the Sleep Heart Health Study,[358] there is a systematic lack of studies that use ambulatory PSG for PM device validation. Compared with the laboratory setting, home recordings are less likely to be influenced by environmental factors including bed comfort, noise, temperature, bed partner, dietary intake and social activities preceding bed time. Moreover, the synchronization procedure allowed us to compare the results in an epoch-by-epoch manner. It may be argued that the unattended setting could increase the proportion of recording failures. However, our study together with others[88] have shown that low failure rate can be achieved when proper protocols are used. Thus, our study design including a simultaneous home PSG setting for PM validation addresses the potential limitations in the current validation studies and can be used as a standard for future protocols in this area.

5.4 Nocturnal BP control in hypertensive OSA patients

Antihypertensive drugs in general have little effect on OSA severity.[270] On the other hand, whether varies classes of antihypertensive agents differ in terms of BP lowing effects in OSA related hypertension is unclear. A randomized study comparing atenolol, amlodipine, hydrochlorothiazide, losartan, and EN, found the strongest nocturnal BP reduction after atenolol whereas severity of SDB was

unaffected by all studied compounds in these hypertensive OSA patients.[359] In study II, we compared the treatment effect of equipotent dosages of DO and EN in OSA patients with hypertension. Nocturnal beat-to-beat BP was better controlled by EN although digital skin vascular regulation was more influenced by DO. Other studies not controlling for sleep apnea reported attenuated nocturnal BP dipping in hypertensive patients after DO[360] and the use of α-blockers was negatively associated with sleep related BP decline.[361] Thus, the issue of optimized antihypertensive therapy in OSA related hypertension remains unsolved. Although sympatholytic agents would have been expected to provide better BP control in OSA patients, this notion was not supported by the effects we recorded after the peripheral α-receptor antagonist DO.

5.5 CV risk assessment by ESH/ESC risk matrix

The CV risk classification matrix used in study V was derived from the World Health Organization – International Society of Hypertension guideline,[317] but has been subsequently extended to indicate the relative risk in two subgroups of non-hypertensive subjects with "normal" or "high normal" BP. The "low", "moderate", "high" and "very high" added CV risk categories have been calibrated to indicate a 10-year risk of CV disease of <15%, 15-20%, 20-30% and >30% respectively according to the Framingham criteria,[362] or a risk of fatal CV disease of <4%, 4-5%, 5-8% and >8% according to the SCORE (systematic coronary risk evaluation) chart.[363] The low/high CV risk threshold used in the ASI algorithm was set to differentiate the "high" and "very high" added CV risk groups from the remaining groups. The rationale for this differentiation was that early interventions are needed in these subjects and the management decision does not differ to any major extent between the "high" and "very high" CV risk groups.

5.6 Sleep state and CV regulation

As early mentioned, sleep is a physiological condition that potentially provides a suitable window to study mechanisms involved in CV regulation.[364] Compared to the daytime condition, there are fewer confounding factors that may affect CV homeostasis during the night rest. For instance, changes of posture, influence of physical activity, stress level, effects of food, caffeine, alcohol intake or smoking are minimally present and therefore negligible during the night-time recording. However, nocturnal rest cannot be regarded as a complete steady state condition as physiological changes do occur during sleep and CV homeostasis may be influenced. For instance, sleep stage transitions may play a role in CV modulation during sleep. We therefore reasoned that a

systematic analysis of cardiac and vascular reactivity during the sleep period may provide information useful for the development of novel tools for CV risk assessment. Respiratory and CV parameters during sleep including oxygen desaturation,[365] BP variation,[366] HR dipping,[367] heart rate variability[368] and arterial vascular tone[369] have all been strongly related to CV morbidity or mortality. In addition, compelling evidence has established a robust association between OSA and CV morbidity as well as mortality.[116,218,219,221] However, traditionally reported indices derived from PSG recordings only show a modest association with hypertension[370] and other forms of CV disease.[192] There is a need for identifying methods, based on easy-to-perform noninvasive techniques, to provide estimates of CV risk in patients investigated for OSA. Such tests would provide a useful tool for identification of patients who are at particular risk for early interventions.

5.7 Physiological variables derived from finger for CV risk prediction

Skin microcirculation has been identified as an area of interest in studies of vascular health and disease.[371] In study IV, we found that certain aspects of nocturnal finger PWA attenuation was associated with daytime BP. Reduced digital vasodilator function assessed by finger reactive hyperemia was reported to be associated with multiple traditional and metabolic CV risk factors.[372] Moreover, measurement of arterial stiffness based on a digital volume pulse wave analysis has been demonstrated to be an useful approach for CV risk assessment in the general population.[373]

Five physiological components were derived from the nocturnal finger pulse oximetry signal for CV risk assessment in study V. The parameters were selected based on their demonstrated relevance in reflecting CV regulatory homeostasis and feasibility as well as extractability from the single photoplethysmographic signal. Variables reflecting cardiac rate variability were identified as the RRPO and the PR-I. The respiratory sinus arrhythmia is considered to reflect vagal-cardiac nerve activity and an increase in the PR reflects the overall cardiac sympathetic activation.[302] Thresholds for these parameters were determined by systematic data fitting in the training set. A similar process was initiated for variables reflecting vascular reactivity and stiffness. These parameters were finally defined as the PWA-I and PPT. We aimed to quantify autonomic events not associated with respiratory and arousal events, hence, only attenuations with less than or equal to a 30% change compared with baseline were included in the analysis. The PPT reflects the transit time of the pressure wave from heart to a peripheral recording site in the

finger and has been proposed as a surrogate measure of pulse wave velocity and arterial stiffness.[374,375] Finally, we opted to introduce a measure of nocturnal oxygenation in the analysis. A 2% oxygen desaturation was chosen for the hypoxia event threshold as it provided the best data fit in the training set. It has been shown previously that 2% oxygen desaturations was closely associated with 4% desaturation events in a sleep lab cohort.[42] Though these five variables were modestly interrelated, the multivariate analysis suggested that each of the five parameters contributed significantly to the model fit and none could be effectively eliminated.

The current data provides strong evidence that an algorithm based on a photoplethysmographic signal offers a reasonable estimate of CV risk as expressed in standard matrix used in clinical medicine. However, it remains to be determined if findings from this cross-sectional analysis can be extended to a prospective analysis. Such studies have been initiated.

5.8 Concluding remarks

The present findings demonstrate that the digital pulsatile wave signal which reflects the blood volume change in the finger vascular bed is modulated by the sympathetic nervous system. The finger PAT signal is periodically attenuated in the immediate post apnea period coinciding with arousal. Acute and chronic administrations of an α-receptor antagonist reverse the PAT attenuation suggesting that the vascular response relies on a sympathoadrenergic α-receptor mediated mechanism. PAT attenuation is a sensitive marker for OSA. With a combined analysis that incorporates PR, oxygen saturation and actigraphy, a portable PAT device can be used for OSA diagnosis with reasonable accuracy. The PAT amplitude is characterized by physiological fluctuations during the overnight sleep recording. The extent of nocturnal episodic PAT attenuation reflects vascular status expressed as diurnal office BP suggesting that assessment of finger PWA signal may provide novel insights into CV physiology and morbidity. This hypothesis is supported by data based on multiple physiological components derived from a single photoplethysmographic signal to provide a CV risk classification. Thus, an algorithm embedded in a routine pulse oximetric signal may enable identification of patients at high CV risk from a single non-invasive overnight recording.

CONCLUSIONS

1. The PAT amplitude periodically attenuates during the post-apnea period coinciding with arousal. The attenuations can be reversed by α-receptor antagonist (phentolamine) infusion. OSA related PAT attenuation is mediated via a sympathoadrenergic α-receptor mechanism.

2. Doxazosin treatment in contrast to equipotent dosages of enalapril attenuates the apnea associated digital vasoconstriction, but provides a poor effect on nighttime beat-to-beat finger BP in patients with OSA and systemic hypertension. Apnea related oxygen desaturation and REM sleep are associated with the magnitude of PAT attenuation.

3. A portable device including PAT, pulse oximetry and actigraphy can be used for OSA diagnosis with reasonable accuracy. A new standard for limited-channel device validation using a simultaneous PSG recording in the home environment is proposed.

4. The degree of PAT attenuation during the night reflecting nocturnal episodic sympathetic activity is quantitatively associated with diurnal BP independent of SDB in a population based cohort.

5. Physiological parameters reflecting cardiac and vascular activity derived from finger pulse oximetry can be incorporated in an algorithm for classification of CV risk rated by the ESH/ESC risk matrix. An assessment based on information from a finger photoplethysmographic signal obtained during sleep is proposed as a novel tool for CV risk classification.

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