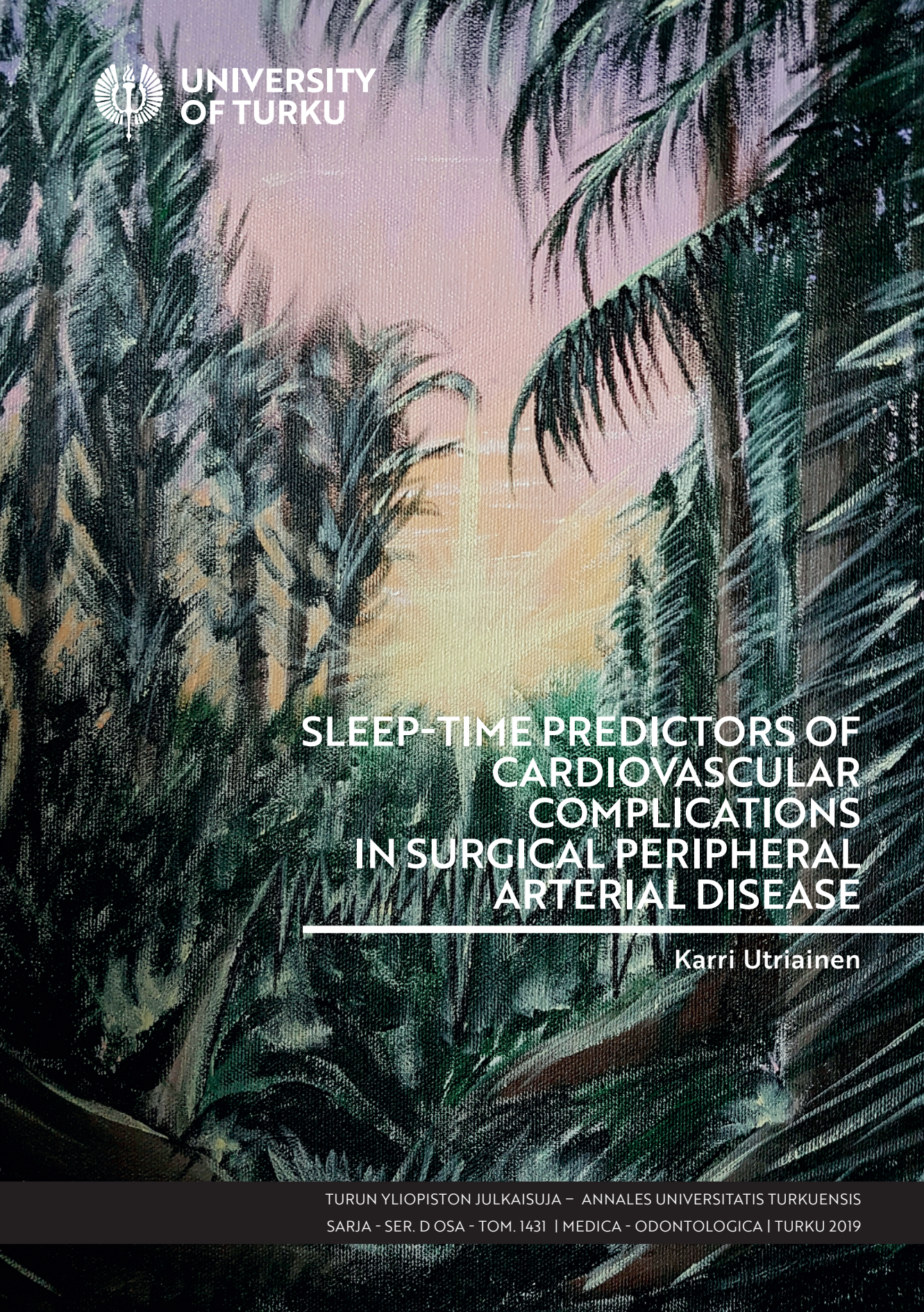

UNIVERSITY OF TURKU

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Karri Utriainen

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To my family

To the Memory of my friend Mikko

ABSTRACT

Karri Utriainen.

Sleep-time predictors of cardiovascular complications in surgical peripheral arterial disease.

University of Turku, Faculty of Medicine, Internal Medicine, Doctoral Programme in Clinical Research, Sleep Research Unit; Division of Medicine, Heart Centre, Division of Perioperative Services, Intensive Care Medicine and Pain Management, Turku University Hospital, Finland.
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Patients with peripheral arterial disease (PAD) undergoing surgical revascularisation are in high risk of postoperative cardiovascular complications and death, due to advancing age and multiple co-morbidities in the population. In addition, PAD needing surgery represents a severe form of systemic atherosclerosis but the exact underlying pathophysiology of acute myocardial infarction (AMI) in these patients is unclear and predicting outcome especially in the long-term is challenging.

Obstructive sleep apnoea (OSA) is increasingly common in the general population and independently associated with various manifestations of cardiovascular disease or their risk factors; OSA is highly prevalent in patients with coronary artery disease (CAD), stroke, hypertension and diabetes. To expand this knowledge, we determined the prevalence and severity (in terms of the apnoea-hypopnoea index, AHI) of OSA in surgical PAD as well as its impact on the incidence of major adverse cardiovascular and cerebrovascular events (MACCE) in this patient group.

Heart rate variability (HRV) reflects fluctuations in sympathetic and parasympathetic activation responsible for neurocirculatory control in various physiological and pathophysiological situations. Depressed HRV is associated with increased cardiovascular morbidity and mortality following AMI and major surgery. In this study, the alterations of nocturnal HRV and their association with the severity of OSA and incidence of MACCE in patients with PAD was assessed, including the fractal correlation properties of HRV. HRV in a control group of 15 healthy subjects was also examined.

Patients scheduled for sub-inguinal vascular surgery (n=84, age 67±9 years) underwent polysomnography and HRV analyses. OSA was detected in 86% of patients and in 56% it was moderate or severe. Age, male gender, depressed left ventricular function and decreasing high density lipoprotein/cholesterol ratio (HDL/Chol) predicted the presence and severity of OSA. The latter two remained significant after adjusting for age and gender. OSA with AHI ≥20/hour, used as a cut-off in the outcome analyses, predicted a higher risk of MACCE (p=0.001) along with pre-existing CAD (p=0.001), decreasing HDL/Chol (p=0.048) and <4 years history of PAD (p=0.018).

HRV was altered in patients with PAD when compared to controls but the time domain measures were mostly unchanged. In the frequency domain, low frequency power was generally lower, high frequency power was mostly higher and fractal correlation was consistently lower. Very low frequency power was increased the most in patients with AHI 10-20/hour when compared to <10/hour while those with AHI ≥20/hour had lower fractal correlation in the morning. Patients suffering a MACCE had lower high frequency power during S3-4 and rapid eye movement sleep.

In conclusion, OSA is associated with worsening atherosclerosis and predicts MACCE after vascular surgery. HRV alterations, although associated with PAD, have limited predictive value.

Keywords: atherosclerosis, peripheral arterial disease, sleep apnoea, heart rate variability

TIIVISTELMÄ

Karri Utriainen

Unenaikaiset sydänkomplikaatioiden ennustetekijät kirurgista hoitoa vaativassa perifeerisessä valtimotaudissa

Turun yliopisto, Lääketieteellinen tiedekunta, Sisätautioppi, Turun kliininen tohtoriohjelma, Unitutkimusyksikkö; Medisiininen toimialue, Sydänkeskus, Totek (Leikkaustoiminta, tehohoito, kivunhoito ja hengitystuki), Turun yliopistollinen keskussairaala, Suomi.
Turun yliopiston julkaisuja, Ser. D, Medica – Odontologica; Painola Oy, Kaarina, Suomi, 2019

Perifeeristä valtimotautia sairastavilla potilailla on suuri leikkauksenjälkeisten sydänkomplikaatioiden riski johtuen yhä iäkkäämmästä väestöstä sekä lukuisista rinnakkaissairauksista. Lisäksi perifeerinen valtimotauti merkitsee vaikea-asteista yleistynyttä ateroskleroosia, mutta sydäninfarktin tarkka syntymekanismi näillä potilailla on epäselvä ja erityisesti pitkän aikavälin ennusteen arviointi on haastavaa.

Obstruktiivinen uniapnea yleistyy väestössä ja sillä on itsenäinen yhteys useisiin sydän- ja verisuonisairauksiin ja niiden riskitekijöihin; uniapnea on erittäin yleinen sepelvaltimotauti-, aivohalvaus-, verenpainetauti- ja diabetespotilailla. Tämän tietopohjan laajentamiseksi tässä tutkimuksessa määritettiin uniapnean esiintyvyys ja vaikeusaste (määrittäjänä apnea-hypopneaindeksi, AHI) vaikea-asteista yleistynyttä ateroskleroosia sairastavilla potilailla sekä sen vaikutus vakavien sydän- ja aivotapahtumien ilmaantuvuuteen.

Sydämen sykevaihtelu kuvastaa autonomisen hermoston toiminnan muutoksia, jotka puolestaan vastaavat verenkierron säätelystä erilaisissa fysiologisissa ja patofysiologisissa tilanteissa. Alentunut sykevaihtelu on yhteydessä lisääntyneeseen kardiovaskulaariseen sairastuvuuteen ja kuolleisuuteen sairastetun sydäninfarktin tai suuren leikkauksen jälkeen. Tässä tutkimuksessa arvioitiin yöllisen sydämen sykevaihtelun muutosten yhteyttä uniapnean vaikeusasteeseen sekä vakavien sydän- ja aivotapahtumien ilmaantuvuuteen, mukaan lukien sykevaihtelun fraktaalikorrelaatio-ominaisuudet. Tutkimuksessa analysoitiin sykevaihtelu myös 15 terveen henkilön vertailuryhmältä.

Nivustason alapuoliseen verisuonileikkaukseen meneville potilaille (n=84, ikä 67±9 vuotta) tehtiin unipolygrafia ja sykevaihteluanalyysi. Uniapnea todettiin 86 %:lla potilaista ja 56 %:lla se oli kohtalainen tai vaikea. Ikä, miessukupuoli, heikentynyt vasemman kammion toiminta ja alentunut HDL-kolesterolin suhde kokonaiskolesteroliin ennustivat uniapneaa ja sen vaikeutumista; 2 viimeksi mainittua säilyivät merkitsevinä ikä- ja sukupuolivakioinnin jälkeen. AHI ≥20/tunti, joka valittiin kynnysarvoksi päätetapahtuma-analyyseihin, ennusti merkitsevästi vakavia sydän- ja aivotapahtumia (p=0.001). Muita merkitseviä tekijöitä olivat sepelvaltimotauti (p=0.001), alentunut HDL-suhde (p=0.048) ja lyhyt (alle 4 vuotta) perifeerisen valtimotaudin kesto ennen leikkaushoidon tarvetta (p=0.018).

Sykevaihtelu oli muuttunut valtimotautipotilailla verrattuna kontrolleihin, mutta aikakenttäparametrit säilyivät lähes ennallaan. Pienitaajuuksinen sykevaihtelu oli yleisesti vähäisempää, suuritaajuuksinen enimmäkseen voimakkaampaa ja fraktaalikorrelaatio johdonmukaisesti heikompaa. Hyvin pienitaajuuksinen vaihtelu oli eniten lisääntynyt AHI 10-20/tunti -alaryhmässä verrattuna AHI <10/tunti -ryhmään, mutta AHI ≥20/tunti -potilailla aamun fraktaalikorrelaatio oli heikompaa. Potilaiden, jotka saivat vakavia sydän- ja aivotapahtumia, suuritaajuusvaihtelu oli heikompaa syvän unen ja vilkeunen aikana.

Johtopäätöksinä todetaan, että uniapnea on yhteydessä vaikeutuvaan valtimotautiin sekä ennustaa vakavia sydän- ja aivotapahtumia verisuonileikkauksen jälkeen sykevaihtelun muutosten ennustearvon ollessa tässä aineistossa hyvin rajallinen.

Avainsanat: ateroskleroosi, perifeerinen valtimotauti, uniapnea, sykevaihtelu

TABLE OF CONTENTS

ABBREVIATIONS

ABI	Ankle-brachial index
AHI	Apnoea-hypopnoea index
AMI	Acute myocardial infarction
ANCOVA	Analysis of covariances
ANOVA	One-way analysis of variances
ANS	Autonomic nervous system
ASV	Adaptive servo ventilation
BMI	Body mass index
BQ	Berlin Questionnaire
CABG	Coronary artery bypass grafting
CI	Confidence interval
cmH2O	Centimetre of water (unit of pressure)
CO2	Carbon dioxide
CPAP	Continuous positive airway pressure
CSA	Central sleep apnoea
cTn-T	Cardiac troponin T
DFA	Detrended fluctuation analysis
DTI	Diffusion tensor imaging
ECG	Electrocardiogram
EDS	Excessive daytime sleepiness
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electro-oculogram
ESS	Epworth sleepiness scale
etCO2	End-tidal carbon dioxide
FA	Fractional anisotropy
HDL	High density lipoprotein
HF	High frequency
HR	Hazard ratio
HRV	Heart rate variability
IQR	Interquartile range
LDL	Low density lipoprotein
LEAD	Lower extremity arterial disease
LF	Low frequency
LTF	Long-term facilitation
LVEF	Left ventricular ejection fraction
MACCE	Major adverse cardiovascular and cerebrovascular event(s)
MRI	Magnetic resonance imaging
ms	millisecond
NNI	Normal-to-normal interval (time between normal ECG R-peaks)

nu	normalised unit
ODI	Oxyhaemoglobin desaturation index
OR	Odds ratio
OSA	Obstructive sleep apnoea
PAD	Peripheral arterial disease
pNN50	Proportion of normal-to-normal RR-intervals of >50 ms in duration
PSG	Polysomnography
PTA	Percutaneous transluminal angioplasty
PTT	Pulse transit time
REM	Rapid eye movement
RMSSD	Root mean square of the sum of successive differences
RRI	RR-interval (time between R-peaks in the ECG)
SaO2 Mean	Mean (nocturnal) arterial oxyhaemoglobin saturation
SaO2 Nadir	Lowest (nocturnal) arterial oxyhaemoglobin saturation
SaO2 T90	Cumulative time below 90 % oxyhaemoglobin saturation
SD	Standard deviation
SDNN	Standard deviation of NNI durations
ULF	Ultra low frequency
VLF	Very low frequency

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications which are referred to in the text with Roman numerals (I – III).

I **Utriainen KT**, Airaksinen JK, Polo O, Raitakari OT, Pietilä MJ, Scheinin H, Helenius HY, Leino KA, Kentala ES, Jalonen JR, Hakovirta H, Salo TM, Laitio TT. Unrecognised obstructive sleep apnoea is common in severe peripheral arterial disease. *Eur Respir J* 2013;41(3):616-620. doi: 10.1183/09031936.00227611.

II **Utriainen KT**, Airaksinen JK, Polo O, Laitio R, Pietilä MJ, Scheinin H, Vahlberg T, Leino KA, Kentala ES, Jalonen JR, Hakovirta H, Parkkola R, Virtanen S, Laitio TT. Sleep apnoea is associated with major cardiac events in peripheral arterial disease. *Eur Respir J* 2014;43(6):1652-1660. doi: 10.1183/09031936.00130913.

III **Utriainen KT**, Airaksinen JK, Polo OJ, Scheinin H, Laitio RM, Leino KA, Vahlberg TJ, Kuusela TA, Laitio TT. Alterations in heart rate variability in patients with peripheral arterial disease requiring surgical revascularization have limited association with postoperative major adverse cardiovascular and cerebrovascular events. *PLoS One* 2018;13(9):e0203519. doi: 10.1371/journal.pone.0203519.

Some additional previously unpublished results are also presented.

1. INTRODUCTION

Peripheral arterial disease (PAD) is a systemic manifestation of atherosclerosis despite that the clinical presentation is typically in the lower extremities. This is perceived to be true even when there are no clinical manifestations in other target organs, e.g. cerebrovascular or coronary artery disease (Hirsch et al. 2001). PAD requiring surgical treatment, in turn, represents a severe form of PAD, i.e. severe systemic atherosclerosis. Consequently, these patients have a high risk of postoperative cardiovascular complications (e.g. myocardial infarction, cardiac death), and their five-year mortality is approximately 30 % (Landesberg et al. 2003; Levy et al. 2011). To predict and prevent this risk, a variety of methods have been employed such as index scores, preoperative cardiac assessments and invasive coronary intervention (Halm et al. 1996; Fleisher et al. 2007; Poldermans et al. 2007). However, the clinical value of these means of risk stratification is limited, partly because the underlying pathophysiology of the cardiac complications is incompletely understood, and predicting the risk of an individual patient to guide clinical decisions remains a challenge (Devereaux et al. 2005).

Sleep-disordered breathing consists of both central and obstructive sleep apnoea (OSA) as well as overlapping forms. In this thesis, OSA is used when obstructive apnoea is the sole or predominant type. Symptomatic OSA syndrome affects 2-4 % of general population (Young et al. 1993) but the overall prevalence of OSA is much higher, up to 23-28 % (Young et al. 2002; Duran et al. 2001). The prevalence of OSA seems to increase in parallel with worsening cardiovascular disease; it is 30-40 % in coronary artery disease (Peker et al. 1999; Mooe et al. 2001) and 60-70 % in patients suffering a stroke (Wessendorf et al. 2000; Rola et al. 2007). The established risk factors of cardiovascular disease such as hypertension and insulin resistance also have a strong association with OSA (Nieto et al. 2000; Peppard et al. 2000). OSA carries a markedly increased risk of cardiovascular morbidity and mortality that may be reversible with continuous positive airway pressure (CPAP) treatment (Marin et al. 2005; Campos-Rodriguez et al. 2012). It has been estimated that the majority of patients with moderate-to-severe OSA are undiagnosed (Young et al. 1997). The recognition and management of pre-existing of OSA in general surgical population is also poor (Singh et al. 2013). Patients with PAD were not studied until recently (Pizarro et al. 2015; Schahab et al. 2017), and neither the prevalence of OSA in surgical PAD nor its effect on postoperative prognosis have been previously determined.

Heart rate variability (HRV) reflects autonomic neurocirculatory regulation and depressed HRV is associated with postoperative myocardial infarction and death following major peripheral vascular surgery (Mamode et al. 2001; Filipovic et al. 2003). Impaired HRV is especially detrimental in patients with coronary artery disease and is a stronger predictor of myocardial ischaemia and mortality than common clinical risk stratification methods (Tapanainen et al. 2002; Laitio et al.

2004). In PAD the behaviour of the various HRV parameters is less clear (Goernig et al. 2008; Leicht et al. 2011), but OSA seems to be associated with HRV alterations indicating increased sympathetic activation and worse prognosis (Narkiewicz et al 1998; Dingli et al. 2003). While depressed nocturnal HRV promotes postoperative myocardial ischaemia following non-cardiac surgery (Laitio et al. 2004), HRV alterations during sleep in patients with surgical PAD and OSA and their impact on long-term morbidity and mortality have not been specifically studied.

In this thesis, we investigated a carefully selected patient population undergoing sub-inguinal vascular surgery to determine the prevalence of occult OSA in surgical PAD as well as its putative predictive value for perioperative cardiac complications and long-term postoperative outcome. The demographic and clinical features of OSA in severe PAD are determined and its possible aetiologies are contemplated. Characteristics of nocturnal HRV during different sleep stages are measured, and the predictive value of HRV for significant OSA and adverse postoperative outcome in this specific patient population is explored.

2. REVIEW OF THE LITERATURE

2.1 Basic physiology of circulation and respiration

Circulation is modified by complex neurohumoral feedback mechanisms that regulate circulatory adaptability and the function of the autonomic nervous system (ANS) is a major factor in the maintenance of cardiorespiratory homeostasis. The sympathetic branch of the ANS exerts powerful hemodynamic effects by increasing peripheral vasoconstriction, heart rate and myocardial contractility. Parasympathetic vagal activation buffers these changes to maintain hemodynamic balance and prevent sympathetic overdrive. (Barrett et al. 2010). Persistent sympathetic activity increases vascular tone, promoting arterial stiffness (Sun 2015).

The chemoreceptors and baroreceptors form a complex system that regulates ANS activity. The chemoreceptors maintain balance of arterial gas tensions, mainly the partial pressures of oxygen (O_2) and carbon dioxide (CO_2). Peripheral chemoreceptors in the carotid body react primarily to hypoxia while central chemoreceptors are located in the brain stem and respond primarily to hypercapnia. Normally, hypercapnia exerts a more powerful excitatory effect on ventilation than hypoxia (Somers et al. 1989). Activation of the chemoreceptors increases sympathetic activity, heart rate and respiratory drive which are buffered by input from the baroreceptors of the aortic arch and pulmonary afferent nerves of the thoracic wall (Barrett et al. 2010). Disturbance of this protective mechanism may cause sympathetic overdrive, predisposing to acute myocardial infarction (AMI), arrhythmias and stroke.

Vascular endothelium plays an important role in the regulation of circulation by promoting vasodilatation via release of nitric oxide. The endothelium also produces numerous other vasoactive agents and inflammatory mediators that control vasomotor tone and blood coagulation (Barrett et al. 2010). Therefore, a healthy endothelium is crucial in the maintenance of normal circulation.

2.2 Pathogenesis and natural course of atherosclerosis

2.2.1 Pathogenesis and pathophysiology, basic concepts

Several risk factors predispose to the development of atherosclerotic vascular damage, starting at an early age (Stary 2000). Positive family history of cardiovascular disease is a major indicator of increased risk in which case primary prevention by lifestyle changes and management of other modifiable factors is especially important (Pandey et al. 2013). Excess dietary intake of saturated fatty acids increases concentration of low-density lipoproteins (LDL), promoting the accumulation of cholesterol in the arterial wall whereas high-density lipoproteins

(HDL) are important in preventing atherosclerosis (Expert Dyslipidemia Panel 2013; Pekkanen et al. 1990). Mechanisms include aggravation of oxidative stress, promotion of endothelial dysfunction and thrombosis (Barter 2011). Numerous other dietary factors along with sedentary lifestyle and lack of physical activity are also detrimental (Mozaffarian 2016; Tikkanen et al. 2018), as well as smoking (Fowkes et al. 1992). Ageing increases arterial stiffness, promoting hypertension and decreasing overall cardiovascular adaptability (Sun 2015). Sustained arterial hypertension is a well-established risk factor as well as diabetes mellitus and insulin resistance (Fowkes et al. 1992; Ishizaka et al. 2003). Furthermore, dyslipidemia, hypertension and insulin resistance are frequently clustered in patients presenting with obesity, constituting the metabolic syndrome that is associated with asymptomatic atherosclerotic changes before the onset of clinical disease (Hunt et al. 2003; Grundy et al. 2005). Importantly, endothelium is prone to damage due to free oxygen radicals; oxidative stress promotes systemic inflammation, oxygenation of lipoproteins and thrombocyte aggregation (Li et al. 2014; Förstermann et al. 2017) and progressive loss of endothelial vasodilatory function begins in the early stage of atherosclerosis (Zeiher et al. 1991).

2.2.2 Advanced systemic atherosclerosis and PAD

2.2.2.1 Pathogenesis and epidemiology of PAD

Atherosclerosis in the iliac or lower extremity arteries commonly manifests in intermittent claudication or critical limb ischaemia resulting in peripheral gangrenes. PAD is commonly referred to as advanced systemic atherosclerosis although such patients do not necessarily have clinical coronary artery or cerebrovascular disease (Hirsch et al. 2001). More specifically, the term lower extremity arterial disease (LEAD) is sometimes used to address vascular disease in leg arteries. All metabolic risk factors of atherosclerosis are also associated with PAD (Fowkes et al. 1992) and markers of vascular inflammation have also been shown to be associated with progression of peripheral atherosclerosis (Tzoulaki et al. 2005). In patients with diabetes mellitus, PAD or LEAD is especially common and is closely connected with a high prevalence of dyslipidemia and hypertension (MacGregor et al. 1999) but the presence and pre-existing complications of diabetes seem to be essential (Wang et al. 2007). Of other risk factors, smoking is even more important than in coronary artery disease and its harmful effect increases with the daily number of cigarettes smoked (Fowkes et al. 1992; Criqui 2001).

The state of lower limb peripheral circulation can be measured with the ankle-brachial index (ABI), i.e. the ratio of blood pressures measured from the ankle and arm. The method is recommended as a non-invasive and inexpensive means for diagnosis (Aboyans et al. 2018). The sensitivity and specificity of the method is high for an angiographically diagnosed stenosis (Criqui et al. 1996). Normally this ratio is 1.0 or more and the commonly used cut-off level for PAD is 0.9 or below (Aboyans et al. 2012); intermittent claudication may or may not be present with mild-to-

moderately decreased ABI while ABI <0.4 indicates critical ischaemia (Aboyans et al. 2018). In diabetic patients, the index may be abnormally high due to mediasclerosis (Aboyans et al. 2012). Toe pressure measurements can be used as a substitute for ABI in diabetic patients (Sahli et al. 2004; Bhamidipaty et al. 2015). A variety of classifications based on symptoms and signs have also been developed such as the Fontaine and Rutherford classifications; these account for the severity of claudication and clinical indicators of critical ischaemia, e.g. resting pain, non-healing ulcers, loss of sensory function and gangrene (Rutherford et al. 1997). A more recent classification system suitable for patients with any signs of critical ischaemia (WIfI = wound, ischaemia and foot infection) combines assessment of wound depth, ABI or toe pressure measurements and presence and severity of infection (Mills et al. 2014) with a higher score indicating greater threat of limb loss and urgent need for revascularisation (Aboyans et al. 2018).

Patients with PAD have suffered from under-recognition, both by diagnosis of the condition *per se* and management of the usual risk factors (Khan et al. 2007) despite it being the third most common manifestation of atherosclerotic disease after coronary artery disease and stroke, and becoming increasingly common worldwide (Fowkes et al. 2013). In a large study, the prevalence of peripheral arterial disease was 29%, and 16% had cardiovascular or cerebrovascular manifestations as well in a population of almost 7000 subjects aged 50 through 69 years with a history of smoking or diabetes (Hirsch et al. 2001). Notably, the management of the conventional risk factors was poorer in patients with peripheral disease only, compared to those with clinical coronary or cerebrovascular manifestations. The epidemiological results are in line with previous data where the prevalence has been 20-30 % in adult or elderly populations (Meijer et al. 1998; Diehm et al. 2004). ABI tends to worsen along with advancing age and this is associated with common manageable risk factors of cardiovascular disease (Kennedy et al. 2005).

PAD has a major impact on cardiovascular morbidity and mortality, independent of other clinical manifestations or risk factors of cardiovascular disease. It has been proposed that a decreased ABI reflects the overall atherothrombotic burden in the vascular tree (Fowkes et al. 2006). There is strong evidence of increased mortality due to cardiovascular causes in patients with severe symptomatic PAD (Criqui et al. 1992; Newman et al. 1999) and low ABI is associated with increased risk of cardiovascular disease independent of other risk factors (Wild et al. 2006). On the other hand, even modest or moderate decreases in ABI (<0.9 or <0.8) have been associated with increased prevalence of cardiovascular disease and incidence of cardiovascular events (Newman et al. 1993; Violi et al. 1996; Heald et al. 2006). Importantly, symptomatic intermittent claudication has a low sensitivity for PAD and was present in a small fraction of patients in most of the studies (Newman et al. 1999; Meijer et al. 1998; Criqui et al. 1996) and the risk of death and cardiac events seems to be the same in asymptomatic disease as in patients with claudication (Leng et al. 1996; Fisher et al. 2008). Furthermore, the increased mortality associated with PAD can be effectively reduced with adequate secondary prevention therapies (Pande et al. 2011). Therefore, a better early recognition of PAD and treatment of

predisposing factors is needed to reduce overall morbidity and mortality in these patients. However, the accuracy of ABI to detect PAD in its early stage may be insufficient (Crawford et al. 2016) and current evidence does not support screening of asymptomatic patients (Alahdab et al. 2015; Guirguis-Blake 2018).

2.2.2.2 Clinical management of PAD

Management of PAD involves identification and treatment of risk factors (hypertension, diabetes), lifestyle intervention (smoking cessation, exercise) and pharmacologic therapy such as antithrombotic drugs and statins (Hankey et al. 2006). Exercise training is essential in the conservative treatment of PAD (Gardner and Poehlman 1995; Watson et al. 2008) and endovascular therapies such as percutaneous transluminal angioplasty (PTA) should always be accompanied with exercise counsel (Mazari et al. 2010). Urgent restoration of circulation by PTA or surgical means is needed in severe cases such as acute or critical ischaemia or when response to conservative treatment is insufficient (Tendera et al. 2011; Gerhard-Herman et al. 2017; Aboyans et al. 2018). However, there seems to be no long-term benefit of endovascular therapy over exercise training in intermittent claudication (Spronk et al. 2009; Pandey et al. 2017). Acetylsalicylic acid alone seems to be less effective than PTA in preventing short and long-term disease progression but the long-term effect on quality of life is controversial (Whyman et al. 1996; Whyman et al. 1997), illustrating the need for more aggressive pharmacologic secondary prevention. However, current evidence supports the use of acetylsalicylic acid and statins as the mainstay of treatment with antiplatelet combination therapy or oral anticoagulation recommended only for certain high-risk patient groups (Dagher and Modrall 2007; Belch et al. 2010; Tendera et al. 2011). Exercise training and endovascular or surgical procedures are all superior to pharmacological therapy in patients with intermittent claudication (Malgor et al. 2015). In patients unsuitable for PTA, surgical procedures, e.g. endarterectomy, femoro-femoral cross-over and femoro-popliteal bypass, can be considered.

The choice between treatment options is made on a case-by-case basis since the evidence from randomised controlled studies comparing different treatment options (including optimised pharmacological therapy) is limited (Antoniou et al. 2017). While a primary PTA may improve walking distance and quality of life more rapidly, there seems to be no clear long-term benefit over successful conservative treatment (Murphy et al. 2012; Malgor et al. 2015). Patients not responding favourably to lifestyle counsel, exercise therapy and medication should be evaluated for endovascular or surgical interventions unless there are excessive risks for postoperative complications (Aboyans et al. 2018). Endovascular therapy is optimal in hemodynamically significant proximal stenoses (Indes et al. 2013; Aboyans et al. 2018) in which maintenance of long-term patency is better than in distal lesions that are also more frequently associated with diffuse disease and limited benefit of invasive therapies (Kashyap et al. 2008; Tendera et al. 2011; Gerhard-Herman et al. 2017). PTA can also be preferred in patients with high surgical risk (Antoniou et al.

2017) and patency after angioplasty can be improved by stent implantation (Kashyap et al. 2008). Surgery may increase long-term amputation-free survival as opposed to angioplasty and is often the best option for extensive femoro-popliteal stenoses but is associated with a higher risk of cardiovascular complications (Adam et al. 2005; Bradbury et al. 2010, Tendera et al. 2011; Aboyans et al. 2018). Finally, amputation remains as the last option for patients with critical ischaemia unsuitable for any means for revascularisation. Regardless of which treatment option is chosen, smoking cessation, exercise training and pharmacological management of risk factors such as dyslipidemia, hypertension and diabetes are essential (Aboyans et al. 2018).

2.3 Epidemiology, pathophysiology and clinical features of OSA

2.3.1 Epidemiology of OSA

OSA is a common health hazard in western societies. It is estimated that approximately 2% of females and 4% of males in general population are afflicted by the condition (Young et al. 1993; Bixler et al. 1998). However, these percentages should be used to refer to the prevalence of OSA syndrome, i.e. symptomatic OSA (e.g. heavy snoring or excessive sleepiness). OSA, in general, is apparently much more common. According to extensive data from Spain, the prevalence of at least mild OSA is 26% in women and 28% in men, aged 30-70 years (Durán et al. 2001). The prevalence of moderate or severe OSA has been estimated to be 1 in 15 (Young et al. 1993). Therefore, OSA becomes rapidly more common with advanced age. OSA is more prevalent in males but it becomes increasingly common in females after menopause (Bixler et al. 2001; Young et al. 2003). Increased sensitivity of modern recording techniques and scoring criteria may result in even higher prevalences of OSA, as shown by the HypnoLaus study, where the prevalence of moderate or severe sleep-disordered breathing (mostly obstructive) was 23.4 % in women and 49.7 % in men (Heinzer et al. 2015). These results suggest that the current AHI criteria defining a clinically relevant OSA disease may need to be revised.

2.3.2 Clinical presentation of OSA

OSA is characterised by repeated episodes of nocturnal hypoxemia, caused by occlusion or significant narrowing of the upper airway as the respiratory lumen collapses due to negative intraluminal pressure. An arousal or awakening is usually required to restore airway patency, resulting in fragmented sleep (Hudgel 1992; Deegan and McNicholas 1995; Patil et al. 2007; Mannarino et al. 2012). Turbulent airflow in a collapsing lumen causes vibration trauma and inflammation in the pharyngeal soft tissue (Hudgel 1992) and promotes snoring, a common symptom of OSA. The prevalence of at least mild OSA has been shown to be approximately one third and one fifth of habitually snoring men and women, respectively (Young et al.

1993). In the Sleep Heart Health Study, 86% of patients with at least moderate OSA were snorers, and those reporting heavy snoring and frequent breathing cessations had an up to four-fold greater likelihood of having at least moderate OSA (Young et al. 2002). Sleep fragmentation due to repeated episodes of hypoxemia, arousals and awakenings causes non-restorative sleep and excessive daytime sleepiness (EDS) (Punjabi et al. 1999; Punjabi et al. 2002). Sleepiness contributes to disability, decreased quality of life and increased risk for motor vehicle accidents.

2.3.3 Pathophysiology of OSA

2.3.3.1 Anatomical factors

Obstructive apnoea results from interactions between a structurally narrow upper airway and decreasing muscle tone during sleep, which is not sufficiently compensated by the phasic contractions of upper airway dilator muscles during inspiratory efforts (Hudgel 1992; Deegan & McNicholas 1995; Patil et al. 2007; Mannarino et al. 2012). The upper airway between the hard palate and the larynx is a collapsible soft tissue tube surrounded by over twenty muscles that maintain its patency during normal breathing. Upper airway patency is dependent on the function of these muscles; the tensor palatini and the tongue that is mostly formed by the genioglossus muscle are the most important determinants of pharyngeal space (Pierce et al. 2007). Therefore, increased collapsibility may result from alterations in the anatomical structures or in the function of the muscles (Polo et al. 1991; Patil et al. 2007).

Narrowing of the upper respiratory lumen may result from several cephalometric characteristics. These include congenital or traumatic anomalies of the nose and palate, shortening of the mandible manifesting as micro- or retrognatia and retro-positioning of the maxilla (Watanabe et al. 2002). Obesity affects airway size by several mechanisms, acting together with the other anatomic features that predispose to OSA (Watanabe et al. 2002). Accumulation of adipose tissue adjacent to the airway is greater in patients with OSA than in body mass index (BMI) -matched controls (Li et al. 2012). While the amount of parapharyngeal fat is related to the severity of OSA (Shelton et al. 1993), the narrowing of the airway is associated with thickening of the lateral pharyngeal walls rather than enlargement of the parapharyngeal fat pads (Schwab et al. 1995).

Taken together, OSA is associated with fat accumulation in the neck that compresses the pharynx mechanically, offsetting the dilatory function of neck muscles and increased neck circumference is the most reliable anatomical feature that predicts OSA in obese individuals (Davies & Stradling 1990; Katz et al. 1990). In morbid obesity, respiratory stress is increased by the sheer weight of the abdominal fat. Supine position promotes occlusion of the upper airway and is therefore detrimental to these patients (McEvoy et al. 1986), possibly by causing epiglottic obstruction (Marques et al. 2017). Finally, lung size in morbidly obese subjects is decreased, resulting in reduced upper airway size as well (Stadler et al. 2010). OSA has a

prevalence of 65-85 % in morbidly obese populations and is likely to be of at least moderate severity (Gasa et al. 2011; Leong et al. 2013; Kositanurit et al. 2018). In the European Sleep Apnoea Database (ESADA) of over 5000 patients with at least mild OSA, approximately 20-30 % were morbidly obese (BMI ≥35 kg/m^2) with 30-50 % presenting with metabolic or cardiovascular abnormalities (Hedner et al. 2011).

2.3.3.2 Functional factors

Activation of the respiratory pump muscles creates a negative pressure that pulls the pharyngeal walls toward each other (Bernoulli phenomenon), compromising airway patency (Badr 1998). Upper airway dilator muscles, including the genioglossus muscle, contract and stabilise the lumen to prevent its collapse (Henke et al. 1991; McGinley et al. 2008). This is facilitated by arterial chemoreceptors responding to increased CO_2 (Onal et al. 1981; Lo et al. 2006). Increased respiratory resistance also stimulates the dilator muscles and the diaphragm in a parallel fashion (Patrick et al. 1982). There is physiological decrease in the tone of these muscles during sleep due to general muscle relaxation that increases upper airway resistance (Mezzanotte et al. 1996; Lo et al. 2007) and the genioglossus muscle requires adequate CO_2 levels to respond to inspiratory loading (Stanchina et al. 2002). In patients with OSA, the compensatory activity of this muscle is compromised during sleep (Mezzanotte et al. 1996; McGinley et al. 2008).

In addition to the respiratory drive to the dilator muscles, conductance of the upper airway is determined by lumen size, resistance to airflow and several other factors that influence collapsibility. First, reduced cross-sectional diameter renders the lumen more collapsible, and obesity is associated with decreased pharyngeal size (Morrell et al. 1998). Second, anatomical factors that increase airway resistance, promote collapsibility as ventilatory drive and negative intraluminal pressure are enhanced. For example, a naturally long pharynx is more prone to occlusion (Yamashiro & Kryger 2012). Third, abnormal shape of the lumen that is seen in apnoeic patients may compromise the ability of the surrounding muscles to maintain patency (Schwab et al. 1993). Finally, obesity is associated with decreased pharyngeal closing pressure and increased airway collapsibility (Genta et al. 2014). Taken together, all factors that influence collapsibility of the upper respiratory tract, define the closing pressure of the lumen. This pressure threshold also depends on sleep stage and is highest (i.e. less negative closing pressure and more collapsible airway) during rapid eye movement (REM) sleep (Carberry et al. 2016). The pressure threshold is approximately 6-8 cmH_2O in healthy subjects; in apnoeic patients or snorers without apnoea it is less negative (around 1.5 cmH_2O), or even positive in severe OSA (Gleadhill et al. 1991; Genta et al. 2014).

Synchronisation of respiratory drive to the upper airway dilators and the respiratory pump muscles plays an important role in the preservation of upper airway patency (Hudgel 1992). Normally, when respiratory drive increases, activation of the pharyngeal dilator muscles precedes that of the diaphragm and thoracic wall muscles (Strohl et al. 1980). Consequently, the upper airway is stabilised before

augmentation of negative intraluminal pressure. While the same appears to be true in patients with OSA during non-apnoeic breaths, desynchronization of this neural drive has been observed during obstructed breathing efforts (Hudgel & Harasick 1990). The activity of the dilator muscles has also been found to oscillate between conditions that predispose to apnoea and those that favour airway patency depending on the force of the inspiratory drive (Hudgel et al. 1987). These mechanisms are in conjunction with the concept that neural drive to respiratory muscles is increased in patients with OSA but imbalance between the activity of respiratory pump muscles and upper airway dilators results in obstruction. In addition, a low arousal threshold seems to predispose to worsening of OSA; arousals are not necessarily needed to maintain or restore airway patency but may promote ventilatory instability instead (Younes 2004).

OSA must be discriminated from central sleep apnoea (CSA) where cessation of breathing is caused by lack of central drive regulated by the respiratory centre. A pure CSA is very rare unless associated with congestive heart failure. However, the difference between OSA and CSA is not always clear-cut. Instead, there is considerable overlapping of the two conditions in which both peripheral and central chemoreceptors are likely to play a role. The respiratory response to CO_2 can be measured with controller gain (i.e. the ratio of change in ventilation to change in CO_2). Other measures are plant gain (i.e. CO_2 response to change in ventilation) and feedback gain (i.e. speed of feedback signal, determined mainly by cardiac output). Loop gain can be calculated from these three measures (i.e. controller gain × plant gain × feedback gain). High controller gain is characteristic to CSA and is related to heart failure and autonomic dysfunction (Solin et al. 2000). Following a collapse of the airway and subsequent arousal, hyperventilation eventually causes hypocapnia, decreasing respiratory drive, promoting either central apnoea or weakening of upper airway muscle tone. Insufficient central drive may therefore maintain obstruction after respiratory efforts recommence. Fitting into this paradigm, decreased CO_2 reserve which is typical in CSA associated with heart failure (Xie et al. 2002) is also characteristic to predominant OSA (i.e. OSA with concomitant central apnoea episodes) as opposed to pure OSA with exclusively obstructive episodes (Xie et al. 2011). In another study, decreased CO_2 reserve was associated with increased controller gain in patients with OSA predisposing to central apnoea (Salloum et al. 2010). Ventilatory control instability (measured with increased loop gain) is also related to the severity of OSA (Younes et al. 2001; Wellman et al. 2004).

2.3.4 OSA as a multifactorial phenomenon

In summary of the above, upper airway muscle tone decreases during sleep and occlusion of the lumen results when this is combined with other factors that compromise airway patency. Arousal restores airway patency but causes sleep fragmentation. Disturbances in oxygen and CO_2 tensions play a crucial role by disrupting central respiratory drive to the dilator muscles. Furthermore, ventilatory response to CO_2 appears to be disturbed in obese patients with OSA in a pattern that

destabilises the function of these muscles (Hudgel et al. 1998). While high loop gain is a primary factor in CSA, it is also included in a number of traits that predispose to OSA, such as pharyngeal anatomy, upper airway muscle responsiveness during sleep and arousal threshold (White 2005). Thus, the pathophysiology of upper airway obstruction in OSA is multi-factorial and involves disturbance in the overall respiratory homeostasis – and in a significant proportion of patients – together with mechanical obstruction. A latter review emphasises that the aetiology of OSA varies between different patient groups; the involved factors include chemical respiratory drive to the pharyngeal muscles, effect of age on airway collapsibility, loop gain, arousal threshold and overall ventilatory control stability (White & Younes 2012). Furthermore, different phenotypes of OSA were observed regarding the age of the patient; either airway collapsibility or sensitive ventilatory control was the dominant pathophysiological feature in older and younger adults, respectively (Edwards et al. 2014).

2.3.5 Diagnosis and treatment of OSA

OSA is conventionally diagnosed with polysomnography (PSG) which has long been considered as the gold standard. The PSG includes the electroencephalogram (EEG), electro-oculogram (EOG), electromyogram (EMG), electrocardiogram (ECG), pulse oximeter for monitoring of arterial oxyhemoglobin saturation and respiratory flow measurement with nasal cannula. This setting allows evaluation of overall sleep quality, minute-by-minute definition of sleep stages, apnoea status and identifies other sleep-related phenomena such as leg movements or teeth grinding (bruxism). Detection of respiratory movement efforts with thoracic and abdominal induction or piezo-electric belts is recommended to differentiate OSA from CSA. Also, the nasal cannula can be used to measure end-tidal CO_2 ($etCO_2$) from expiratory airflow (American Academy of Sleep Medicine Task Force 1999).

Apnoea and hypopnoea are identified from the respiratory flow signal and the apnoea-hypopnoea index (AHI) is expressed as the number of events per hour of sleep. An AHI >5/hour is the most used cut-off level in current literature. The American Academy of Sleep Medicine classifies sleep apnoea as mild (AHI 5-15/hour), moderate (AHI 15-30/hour) and severe (AHI >30/hour) with the according thresholds in the AHI (American Academy of Sleep Medicine Task Force 1999). The nature of sleep apnoea is defined as obstructive or central according to which kind of apnoea episode is predominant. The gold standard to distinguish obstructive and central apnoea episodes is to measure the changes of intrathoracic pressure via an oesophageal pressure transducer (Baydur et al. 1982). To avoid the invasiveness of this technique, this is usually done by utilizing piezo-electric or induction belts that measure movements of the abdominal and thoracic wall to detect respiratory efforts and progressive desynchronisation between the movements of the abdominal wall and the rib cage (Lévy et al. 1992). Another non-invasive method is to measure the pulse transit time (PTT) from the R-peak of the electrocardiogram and the peripheral pulse wave detected with a pulse oximeter. This technique has been

validated against the gold standard for differentiation of both obstructive apnoea and hypopnoea episodes from central ones (Argod et al. 1998; Argod et al. 2000).

Currently, the most widely applied treatment for moderate-to-severe OSA is CPAP and its variations such as bi-level positive airway pressure and adaptive servo ventilation (ASV) therapies. A CPAP device maintains a positive airway pressure by delivering constant airflow via nasal or facial mask to the upper airway. The airway pressure serves as a pneumatic splint that maintains upper airway patency throughout the respiratory cycle during sleep (Sullivan et al. 1981). Numerous studies have shown that CPAP ameliorates sleep deprivation, decreases the subjective symptoms (snoring, EDS) and improves quality of life (Yamamoto et al. 2000; Siccoli et al. 2008; Avlonitou et al. 2012).

2.4 Sleep apnoea and cardiovascular disease

2.4.1 Epidemiology of OSA in cardiovascular disorders

2.4.1.1 OSA and clinical cardiovascular disease

OSA is associated with a plethora of cardiovascular co-morbidities and among patients suffering from various manifestations of atherosclerotic disease its prevalence is much higher than in general population. Approximately 30-40 % of patients with coronary artery disease (Peker et al. 1999; Mooe et al. 2001) and 60-70% of patients with stroke or transient ischaemic attack (Wessendorf et al. 2000; Rola et al. 2007; Joo et al. 2011) appear to have OSA. There is also evidence that OSA precedes incident stroke, increases mortality (Yaggi et al. 2005; Campos-Rodríguez et al. 2014) and that OSA hampers recovery from ischemic stroke (Yan-fang & Yu-ping 2009). Another study showed a high prevalence (ca. 64 %) of moderate or severe OSA (AHI >15/hour) in patients undergoing percutaneous coronary intervention or coronary artery bypass grafting (Glantz et al. 2013). In the Sleep Heart Health Study, OSA carried a 58 % and 68 % increased risk of incident heart failure and coronary artery disease, respectively (Gottlieb et al. 2010). This effect was seen only in men with severe OSA, compared to those with no OSA. In the Wisconsin Sleep Cohort Study, the incidence of coronary artery disease was 2.6 times higher in patients with severe untreated OSA than in those without (Hla et al. 2015). Moreover, patients with OSA have been described to be prone to myocardial ischaemia even in the absence of clinical coronary artery disease (Hanly et al. 1993). Increased overall and all-cause mortality related to OSA in cardiovascular and cerebrovascular disease has been observed in two meta-analyses (Ge et al. 2013; Xie et al. 2014).

2.4.1.2 OSA and cardiovascular risk factors

OSA has been shown to be independently associated with several key risk factors of atherosclerosis. Hypertension in patients with OSA is not caused by obesity alone as shown in large-scale population-based studies (Grote et al. 1999; Peppard et al. 2000; Nieto et al. 2000). It has also been postulated that multi-drug dependent or drug-resistant hypertension is independently associated with OSA (Lavie et al. 2001; Logan et al. 2001). The pathophysiological interaction between hypertension and OSA involves hypoxia-mediated sympathetic activation, oxidative stress, systemic inflammation and endothelial dysfunction (Fletcher 2003; Jelic et al. 2008). Activation of the renin-angiotensin-aldosterone system is also likely to play a role in the development of hypertension, and may also lead to worsening of OSA via airway narrowing due to fluid retention (Pratt-Ubunama et al. 2007; Dudenpostel et al. 2012). Finally, improvement in both nocturnal and 24-hour blood pressure has been achieved by CPAP treatment in patients with OSA and resistant hypertension (Martínez-García et al. 2013).

It has been a matter of controversy whether insulin resistance and type 2 diabetes mellitus are independently associated with OSA or share obesity as a common risk factor (Sharma et al. 2007). However, other studies have been able to demonstrate impaired glucose tolerance in patients with OSA independent of obesity (Ip et al. 2002; Punjabi et al. 2002). Afterwards, increased insulin resistance was shown in obese OSA patients independent of obesity but associated with EDS instead (Barcelo et al. 2008). In the Sleep Heart Health Study, higher prevalence of impaired glucose tolerance in OSA patients was also confirmed in both obese and non-obese population (Seicean et al. 2008). In a more recent study, metabolic syndrome including insulin resistance was highly prevalent (51 %) in patients with OSA and increased with the severity of OSA, irrespective of EDS (Bonsignore et al. 2012).

2.4.1.3 Asymptomatic OSA

It is not fully established whether the presence of EDS is relevant in determining the cardiovascular risk caused by OSA (Kendzerska et al. 2014). In patients with heart failure or stroke, EDS is less frequent and does not adequately predict OSA (Arzt et al. 2006; Arzt et al. 2010). While EDS is associated with OSA severity, diabetes and carotid atherosclerosis (Saletu et al. 2008), early signs of atherosclerosis have also been demonstrated in minimally symptomatic and asymptomatic OSA (Kohler et al. 2008; Drager et al. 2010). However, one cohort study showed increased overall mortality in older adults with OSA only in the presence of EDS (Gooneratne et al. 2011). The controversies may result from different patient populations; subjects referred to a sleep laboratory due to suspected OSA are more likely to have EDS as well.

2.4.2 Consequences of OSA in cardiovascular disease

2.4.2.1 OSA-related coronary vascular events

Concomitant OSA is very common in patients presenting with acute coronary events with a prevalence of up to 50-60 % in AMI and acute coronary syndrome (Lee et al. 2009; Lee et al. 2011; Schiza et al. 2012). However, some studies have shown a reduction in the prevalence of OSA during follow-up after clinical recovery from the acute phase of a coronary event (Skinner et al. 2005; Schiza et al. 2012; Buchner et al. 2012). These findings may explain earlier results showing no increase in mortality associated with OSA diagnosed concurrently with acute coronary syndrome (Mehra et al. 2006). An early study showed that even mild OSA is independently associated with AMI in surviving (PSG performed post-AMI) male patients (Hung et al. 1990). Furthermore, OSA predicts poor prognosis and impaired recovery of left ventricular function following AMI as well as increased overall mortality in coronary artery disease (Peker et al. 2000; Nakashima et al. 2006; Xie et al. 2016). In addition, poorer clinical outcome following percutaneous coronary intervention, including less reduction in infarct size and increased risk of new coronary events has been demonstrated (Yumino et al. 2007; Buchner et al. 2014; Lee et al. 2016). Poor recovery following coronary events may relate to severe endothelial dysfunction that has been shown in patients with moderate-to-severe OSA (Sert Kuniyoshi et al. 2011).

2.4.2.2 Mechanisms of OSA-related cardiovascular disease

OSA is associated with sympathetic activation and other pathophysiological mechanisms that are also the key factors in the development of cardiovascular disease, including pressor surges, oxidative stress, systemic inflammation and endothelial dysfunction (Somers et al. 1995; Kato et al. 2000; Jelic et al. 2008). Intermittent hypoxia is a potential cause for sympathetic activation as OSA has been shown to induce adrenergic overdrive in metabolic syndrome via hypoxia-mediated chemoreceptor activation with impaired baroreflex control (Grassi et al. 2010). Tonic chemoreflex activation and augmented autonomic chemoreflex responses have been demonstrated in OSA and metabolic syndrome (Narkiewicz et al. 1998; Narkiewicz et al. 1999; Trombetta et al. 2013). The effect of repeated nocturnal hypoxia is aggravated by deficient parasympathetic inhibition due to lack of normal lung inflation and persists during wakefulness (Morgan 1996; Leuenberger et al. 2005; Mansukhani et al. 2014). The risk of AMI, arrhythmias and stroke are likely to be increased if pressor surges are insufficiently countered by the baroreflex. Interestingly, the incidence of AMI in patients with OSA peaks from 6 a.m. to 12 a.m. as opposed to the early morning hours in the general population (Kuniyoshi et al. 2008).

In addition to the ANS dysfunction, several other mechanisms have been identified. These include reduced stroke volume as well as intra-thoracic pressure swings

caused by forced respiratory efforts that increase left ventricular afterload, impair diastolic filling and predispose to left ventricular hypertrophy (Bradley et al. 2001). Moreover, hypoxemia enhances platelet aggregation (Bokinsky et al. 1995), promotes oxygenation of lipoproteins (Luyster et al. 2012) and systemic inflammation via production of oxygen radicals (Yokoe et al. 2003; Ryan et al. 2005), contributing to endothelial dysfunction. Accordingly, oxidative stress has been postulated as the key factor and the unifying paradigm underlying the cardiovascular co-morbidities and metabolic disorders associated with OSA (Lavie 2009; Lavie & Lavie 2009). Furthermore, OSA combined with metabolic disturbances has been suggested to be a pivotal factor in the overall pathogenesis of atherosclerosis (Lorenzi-Filho & Drager 2007).

2.4.3 Sleep-disordered breathing and heart failure

Congestive heart failure is also associated with OSA (Ferrier et al. 2005). In addition to the detrimental effect of intermittent hypoxia on left ventricular systolic function, OSA increases the risk of atrial fibrillation, further contributing to decreased cardiac output (Gami et al. 2004; Gami et al. 2007). However, central apnoea is more characteristic to heart failure (Vazir et al. 2007) and CSA seems to correlate with its clinical severity (Oldenburg et al. 2007; Javaheri et al. 2016). The presence of Cheyne-Stokes respiration predicts mortality in severe heart failure with LVEF <30 % (Brack et al. 2007) and AHI ≥30/hour is an independent prognostic factor in patients with LVEF ≤35 % (Lanfranchi et al. 1999). Imbalance in arterial gas tensions and decreased body stores of oxygen and CO_2 are essential in the pathophysiology of Cheyne-Stokes respiration. CSA is very rare in general population and has a prevalence of less than 1 % in the absence of heart failure (Bixler et al. 1998; Bixler et al. 2001). Overlapping of OSA and CSA may occur in patients with heart failure with varying predominance (Javaheri et al. 1998; Javaheri et al. 2017). When the predominant type of apnoea is obstructive, moderate OSA (AHI ≥15/hour) increases mortality but the benefit of treatment is not clear (Wang et al. 2007).

2.4.4 Effect of treatment of OSA and CSA in cardiovascular disease

2.4.4.1 Effect of CPAP and ASV therapies

The deleterious effects of OSA in symptomatic patients can potentially be attenuated with CPAP therapy. In patients with severe OSA (AHI ≥30/hour), an observational study showed that CPAP reduces the risk for fatal and non-fatal cardiovascular events (Marin et al. 2005). Women with severe OSA also have an increased risk of cardiovascular death that was alleviated with CPAP treatment in another observational study (Campos-Rodríguez et al. 2012). Other thresholds for apnoea severity have also been applied, e.g. AHI ≥15/hour and AHI ≥20/hour (Cassar et al. 2007; Martínez-García et al. 2009). Another study showed a correlation between the

AHI and cardiac structural and functional deterioration that was reversible with CPAP in patients with hypertension and severe OSA but without clinical cardiac disease (Shivalkar et al. 2006). Elderly patients with severe OSA also achieve reduced risk of cardiovascular death when adhering to CPAP, i.e. when it is used for more than four hours every night (Martínez-García et al. 2012).

The data showing the benefit of CPAP have been obtained from observational or retrospective studies but there is a shortage of confirming results from randomised controlled trials (McEvoy et al. 2016; Peker et al. 2016). This problem has also been acknowledged in recent meta-analyses but the lack of efficacy may relate to insufficient adherence to CPAP (Abuzaid et al. 2017; Wang et al. 2018). Nevertheless, CPAP lowers blood pressure in severe OSA and resistant hypertension which is likely to reduce cardiac risk (Martínez-García et al. 2013; Bratton et al. 2014). The benefit may depend on the adherence to treatment. Indeed, there seems to be a favourable effect on cardiac outcome with a CPAP usage of more than four hours per night (Peker et al. 2016; Abuzaid et al. 2017). Results from patients with heart failure and predominant central apnoea are even more controversial. CPAP decreases short-term mortality in heart failure patients with CSA (Sin et al. 2000) but there is no evidence of improvement on long-term survival despite attenuation of the AHI, left ventricular dysfunction and sympathetic activation (Bradley et al. 2005). Another study suggested a potential benefit of early CPAP for CSA (Arzt et al. 2007) but ASV (i.e. adjusted CPAP based on the detection of apnoeas) seems to *increase* mortality in patients with heart failure and CSA (Cowie et al. 2015; Eulenburg et al. 2016; Woehrle et al. 2017). The mechanism of the increased mortality associated with ASV therapy in heart failure remains an open question.

2.4.4.2 Treatment effects of CPAP in asymptomatic patients

In controlled studies with nasal and sham CPAP, daytime vigilance or blood pressure could not be improved with CPAP in asymptomatic (without sleepiness) subjects (Barbé et al. 2001; Robinson et al. 2006). In a later trial, the overall cardiovascular risk was not reduced by CPAP in minimally symptomatic OSA patients (Craig et al. 2012). Another randomised controlled study showed no reduction in the incidence of hypertension or cardiovascular events in non-sleepy OSA patients treated with CPAP (Barbé et al. 2012). A more recent meta-analysis showed that lipid profiles in patients with OSA can be improved with CPAP therapy and this effect is most prominent in moderate to severe OSA with daytime sleepiness (Lin et al. 2015). However, there seems to be no effect on inflammatory markers (Stradling et al. 2015). Thus, systematic screening for OSA is not currently encouraged due to the limited clinical applicability of current screening tools and the modest effect on most outcomes (Jonas et al. 2017).

2.4.5 OSA and postoperative complications

OSA is recognized to carry a remarkable risk of various postoperative complications. However, the available data are mostly limited to respiratory complications or surrogate endpoints. These include prolongation of intensive care, or respiratory complications such as pulmonary atelectasis and transient desaturations requiring reintubation or supplemental oxygen (Gupta et al. 2001, Hwang et al. 2008; Mador et al. 2013). Perioperative CPAP therapy and postoperative supplemental oxygen have been tried to improve oxygenation and reduce the AHI postoperatively (Liao et al. 2013; Liao et al. 2017). Some studies have also demonstrated a decrease in postoperative cardiovascular and cardiopulmonary complications by CPAP (Mutter et al. 2014; Abdelsattar et al. 2015), while other trials have failed to do so (Mador et al. 2013; Nagappa et al. 2015). Combination of different screening and monitoring tools may be useful in identifying patients suitable for postoperative management of OSA (Gali et al. 2009). The American Society of Anesthesiology Task Force has advocated the use of CPAP in the preoperative management of surgical patients with severe OSA (Gross et al. 2006). However, there is insufficient evidence whether this would improve postoperative outcome in these patients. Similar recommendations have been given in later Task Force reports; the evidence of a beneficial effect of CPAP therapy for the prevention of these events, preceding or following surgery, is controversial (Chung et al. 2016; Opperer et al. 2016).

2.5 Postoperative cardiovascular complications in advanced atherosclerosis

2.5.1 Postoperative complications in non-cardiac surgery

Cardiac complications (i.e. AMI, cardiac arrest, cardiac death) following non-cardiac surgery remain an issue of remarkable clinical impact. This is especially true in patients undergoing major vascular surgery where the incidence of postoperative myocardial infarction is high. Approximately 10-20 % and up to 30 % of patients undergoing sub-inguinal vascular surgery suffer a perioperative or postoperative AMI (Landesberg et al. 2003; Levy et al. 2011) and myocardial ischaemia occurs in an even higher proportion (Mangano et al. 1990). Perioperative AMI accounts for approximately one third of in-hospital cardiac deaths and predicts new cardiovascular events also in the six months following surgery (Devereaux et al. 2005). The 30-day mortality of these patients is approximately 10-25 % (Badner et al. 1998, Devereaux et al. 2005, Devereaux et al. 2011). Furthermore, the overall five-year mortality of patients undergoing sub-inguinal vascular surgery is approximately 30 %, mostly due to cardiac complications (Conte et al. 2001; Landesberg et al. 2003; Levy et al. 2011).

The high cardiac mortality following vascular surgery relates to the fact that these patients typically have a severe systemic atherosclerosis, as reflected by the presence of PAD itself. In an early study, pre-existing clinical coronary artery disease was a

major predictor of postoperative AMI in non-cardiac surgery (Ashton et al. 1993). However, subclinical coronary artery disease is common in patients undergoing vascular surgery and especially in those with PAD (Hirsch et al. 2001). Furthermore, postoperative myocardial ischaemia is frequently asymptomatic and silent AMI carries the same prognostic significance as symptomatic AMI (Deveraux et al. 2005; Devereaux et al. 2011). Therefore, more advanced risk stratification methods are needed to detect the patients at the highest risk of postoperative complications.

2.5.2 Prediction and prevention of postoperative cardiac complications

2.5.2.1 Current means for risk stratification and prevention

To recognize patients at high risk of major cardiac complications, a variety of risk stratification methods have been employed. These involve risk scores based on presence and severity of underlying diseases such as diabetes, renal or heart failure and the overall severity of atherosclerosis. One of the most used scores is the Lee Revised Cardiac Risk Index (Lee et al. 1999). Based on these indices, patients can be referred to preoperative coronary revascularisation. Improvement on long-term survival has been demonstrated in intermediate-risk patients (Landesberg et al. 2007) and there is also evidence of possible benefit in high-risk patients (Boersma, 2001). Left ventricular ejection fraction (LVEF) can provide relevant information in patients determined to be at high risk according to clinical criteria, but its usefulness has been questioned especially in low-risk patients (Halm et al. 1996; Rohde et al. 2001). Cardiac biomarkers such as natriuretic peptides can independently predict perioperative myocardial ischaemia and short-term postoperative cardiac events (Feringa et al. 2007; Karthikeyan et al. 2009). However, randomised trials have shown that preoperative coronary revascularisation does not improve outcome in intermediate-risk or high-risk patients, compared to conservative treatment (pharmacologic therapy) and can be omitted (Poldermans et al. 2006; Poldermans et al. 2007; Schouten et al. 2009). Accordingly, the controversies in the data regarding the benefit of interventions based on preoperative testing compromise the usefulness of currently used means of risk stratification as a basis for clinical decisions.

2.5.2.2 Role of pharmacological therapy

Some studies have shown that preoperative administration of beta-blocker therapy reduces the probability of postoperative cardiac events (Poldermans et al. 1999) and the protective effect of beta-blockers may even extend to two years after successful surgery (Poldermans et al. 2001). However, concerns have been raised over these studies and the applicability of their results is being questioned. Statins may also be beneficial (O'Neil-Callahan et al. 2005; Feringa et al. 2007). The possible cardioprotective effect of beta-blockers, if any, may require tight control of heart rate which is likely to predispose to side effects (Feringa et al. 2006; Beattie et al. 2008). In addition, the benefit of these drug therapies has mostly been limited to prevention

of non-fatal events with no evidence of decreased overall mortality making any recommendation of routine preoperative beta-blocker therapy questionable (Devereaux et al. 2005; Bangalore et al. 2008). Indeed, a large randomised controlled trial showed that patients on metoprolol treatment had an increased overall mortality and incidence of stroke (in a 30-day follow-up) despite suffering less perioperative myocardial infarctions (Devereaux et al. 2008). Consequently, perioperative use of beta-blocker in patients of any age group undergoing non-cardiac surgery has been discouraged due to lacking evidence of any real benefit and high risk of side effects (Mostafaie et al. 2015; Blessberger et al. 2018). Perioperative administration of clonidine and acetyl salicylic acid have also been tried with no apparent benefit (Devereaux et al. 2014; Devereaux et al. 2014).

2.5.2.3 Open questions and future prospects

The major difficulty hindering identification of patients at risk of peri- and postoperative cardiac events is the lack of profound understanding of the underlying pathophysiology. While the pathogenesis of non-operative AMI and coronary artery disease is well understood, such is not the case with peri- and postoperative AMI since findings in patients having suffered a fatal and non-fatal AMI are controversial (Devereaux et al. 2005). Whereas two thirds of fatal perioperative AMIs involve a left main or three-vessel disease, a plaque rupture or intra-arterial thrombosis is evident in only one third of the cases (Dawood et al. 1996; Cohen et al. 1999). Furthermore, non-fatal AMI occurs frequently without clinically relevant coronary stenosis (Ellis et al. 1996). These observations implicate that several other factors than the severity of coronary artery disease *per se* must have a crucial role in the pathogenesis of postoperative cardiac complications in patients undergoing non-cardiac surgery. Therefore, more knowledge of the underlying pathophysiology and novel cost-effective risk stratification methods is needed.

There is evidence that PAD is associated with small artery disease of the brain in the absence of clinical cerebrovascular disease (Longstreth et al. 2005). White matter lesions detected with magnetic resonance imaging (MRI) of the brain are common in patients with decreased ABI (Bots et al. 1993), implying that PAD is associated with cerebrovascular disease. Diffusion tensor imaging (DTI) is a novel MRI technique that assesses the microstructural integrity of brain white matter tracts, permitting quantitative measurements such as fractional anisotropy (FA). Decreasing FA reflects axonal loss (Jones et al. 1999) even in patients with no ischaemic changes in conventional MRI (O'Sullivan et al. 2001). These disruptions precede the development of lesions in conventional MRI (de Groot et al. 2013) and predict clinical stroke (Evans et al. 2016). Moreover, decreasing FA values are associated with increased morbidity and mortality in patients with PAD (Virtanen et al. 2014; van der Holst et al. 2016). In addition, the risk factors and early stages of atherosclerosis are associated with white matter microstructural damage (Segura et al. 2009; Gons et al. 2010; Falvey et al. 2013). Taken together, DTI has potential

value for risk stratification in patients with cardiovascular disease, the clinical utility of which remains to be defined.

2.6 Heart rate variability

2.6.1 Basic concepts of heart rate dynamics

Decreased heart rate variability (HRV) and baroreflex function have been introduced as prominent risk factors of cardiovascular morbidity and mortality (Kleiger et al. 1987; Farrell et al. 1991; Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology 1996). In normal physiology, blood pressure surges caused by internal or external triggers are buffered by the baroreceptors. Consequently, parasympathetic vagal activation decreases heart rate and maintains blood pressure in a safe window (Kirchheim 1976). Thus, heart rate and blood pressure are normally regulated by complex interactions of the sympathetic and parasympathetic branches of the ANS; in cardiovascular disease, these mechanisms are disturbed (La Rovere et al. 2008). As a result, pressor surges are inadequately countered by the baroreceptors, and heart rate is maintained at unsuitable levels. The resulting predomination of sympathetic tone is potentially deleterious to patients with compromised cardiovascular adaptability, predisposing to myocardial ischaemia, AMI, arrhythmias and cardiac death (La Rovere et al. 1998). Baroreceptors of the carotid body are important in the baroreflex control of autonomic tone (Smit et al. 2002); HRV reflects efferent outflow (sympathetic vs. vagal) of the ANS to the heart (Malliani et al. 1991). Therefore, analysis of HRV can be used to assess autonomic dysfunction in various pathophysiological conditions although it must be acknowledged that alterations in HRV are not generated by sympathetic and vagal activation alone (Malik et al. 1993).

2.6.2 Assessment of HRV

2.6.2.1 Time and frequency domain methods

Conventional assessment of HRV includes time and frequency domain analyses (Laitio et al. 2007). Statistical time domain measurements include standard deviation of the interval between normal R-peaks (SDNN) in the ECG (RR-interval, RRI of which normal-to-normal interval, NNI, is most often used), root mean square of the sum of successive differences (RMSSD) between adjacent RRI (i.e. beat-to-beat variability) and proportion of NNI >50 ms in duration (pNN50). In general, decreasing values in these parameters reflect depressed HRV due to compromised vagal heart rate control. While the total power of the HRV spectrum reflects overall autonomic activity, different contributions of the ANS as well as humoral and circadian rhythms are illustrated in the HRV spectrum as high frequency (HF; 0.15-0.4 Hz), low frequency (LF; 0.04-0.15 Hz), very low frequency (VLF; 0.003-0.04 Hz) and ultra-low frequency (ULF; ≤0.003 Hz) oscillations in heart rate. The power

of each frequency domain is expressed in the spectrum as the square of milliseconds (ms^2). HF reflects rapid heart rate oscillations resulting from parasympathetic activation and a major part of HF power consists of physiologic sinus arrhythmia caused by normal respiration. LF, VLF and ULF consist of slow changes during longer periods due to sympathetic activation, metabolic and endocrinologic activity, circadian rhythms and temperature regulation. Of these, VLF and ULF are best determined from ECG recordings of several hours or days in duration (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology 1996). The LF/HF ratio is commonly used to express predominance of either aspect of ANS since LF and HF are (supposedly) mainly affected by sympathetic and vagal activity, respectively (Malliani et al. 1991). However, it does not reflect the absolute degree of ANS activity but rather the relative strength of sympathetic activity to parasympathetic tone (i.e. sympathetic activation increases the ratio) to a limited extent. In addition, both sympathetic and parasympathetic activation contribute to the LF component.

Decreased HRV measured with the spectral parameters mentioned above predict increased mortality as late as one year following an AMI (Bigger et al. 1993). Later studies have shown that time domain measures of HRV lose their prognostic value in patients with AMI when early revascularisation is performed (Compostella et al. 2016; Compostella et al 2017) whereas in an earlier study SDNN and LF measures retained some short-term predictive value (Coviello et al. 2013). The normalised units (nu) of LF and HF (ratio of the respective spectral power and total power, excluding VLF, multiplied by 100) are sometimes used instead of the absolute powers because they are less affected by the simultaneous change in total power (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology 1996).

2.6.2.2 Non-linear methods

Normal heart rate is known to uphold fractal dynamics, i.e. short-term changes reflect changes in the long term (Yamamoto & Hughson 1994; Yamamoto et al. 1995). In disease states, such as severe heart failure, the fractal pattern disintegrates (Goldberger et al. 2002). This may result in completely random fluctuation of heart rate and poor cardiovascular adaptability to pressor surges and other detrimental events, increasing risk of AMI and sudden death. Complete obliteration of fractal correlation (loss of self-similarity) is known to occur in severe congestive heart failure (Poon & Merrill 1997). The adherence of HRV to fractal dynamics can be calculated by detrended fluctuation analysis (DFA) and is expressed by a fractal scaling exponent alpha (Peng et al. 1995). Alpha 1 reflects short-term fractal correlation properties of heart rate. A value of 1 represents high fractal correlation whereas low values (i.e. close to 0.5) reflect increasing randomness in heart rate and risk of ventricular arrhythmias. A scaling exponent value reflecting strong fractal correlation is a characteristic feature of complex physiological systems regulated by intricate feedback mechanisms (i.e. a healthy cardiovascular system). Conversely,

increasing randomness is associated with poorer outcome in coronary artery disease following AMI (Tapanainen et al. 2002) and bypass grafting (Laitio et al. 2000). Loss of fractal heart rate dynamics also independently predicts mortality in patients with post-AMI depressed LVEF (Mäkikallio et al. 1999; Huikuri et al. 2000) and even slightly decreased alpha 1 has been shown to be associated with cardiac death in a general elderly population (Mäkikallio et al. 2001). Fractal correlation of HRV during sleep has not been previously studied in patients with PAD undergoing vascular surgery.

Other non-linear methods to quantify the regularity and predictability of an RRI time series are approximate entropy and sample entropy. Entropy reflects the likelihood that different epochs of any given length in a time series remain statistically similar to each other. Greater likelihood of similarity means low entropy (0.7 - 1.0) and lesser likelihood yields higher entropy values (close to 2.0). Sample entropy is the most reliable of these parameters. In short, it quantifies the irregularity of an RRI time series with increasing entropy reflecting higher complexity due to feedback regulation (Richman & Moorman 2000).

2.6.3 HRV and postoperative morbidity and mortality

Several earlier studies have shown that decreased HRV is linked with autonomic dysfunction and associated with cardiac death or myocardial infarction following major surgery or trauma (Filipovic et al. 2003; Mamode et al. 2001; Cooke et al. 2006). Furthermore, studies involving patients with cardiovascular disease and cohort studies with elderly subjects have suggested HRV to be a more powerful predictor of mortality than established clinical parameters such as decreased LVEF (Tsuji et al. 1994; Bauer et al. 2006). Other studies have linked decreased HRV with haemodynamic instability during anaesthesia and surgery (Hanss et al. 2006). In patients undergoing coronary artery bypass grafting (CABG), studies have shown that HRV (with all measurement methods, including DFA) decreases immediately after surgery and recovers gradually within 6-12 months (Kuo et al. 1999; Laitio et al. 2006). Another study (Lakusic et al. 2013) showed that decreased HRV persisting after CABG was associated with higher mortality during a mean follow-up of three years but this is contradicted by previous reports (Milisevic et al. 2004; Stein et al. 2004). Nevertheless, impaired HRV is associated with postoperative myocardial ischaemia and prolonged need of intensive care following CABG (Laitio et al. 2000; Laitio et al. 2002). Furthermore, of the nonlinear measurements of HRV, particularly DFA has been shown to be superior to time and frequency domain methods (Laitio et al. 2000; Wu et al. 2005).

Impaired nocturnal HRV has also been shown to promote postoperative myocardial ischaemia in patients undergoing surgery due to hip fracture, emphasising the cardiovascular risk associated with sleep (Laitio et al. 2004). Investigations on long-term outcome following non-cardiac surgery have shown that depressed HRV measured perioperatively is an independent predictor of one-year mortality (Filipovic et al. 2003).

2.6.4 Open issues

Analysis of HRV provides means for evaluating autonomic dysfunction that is essential in the development of cardiovascular disease. However, the clinical feasibility of HRV to guide clinical decisions is limited because the assessment of HRV from 24-hour recordings is time-consuming and there are no reliable tools for automatic editing of data and calculation of HRV parameters. Furthermore, several other factors than atherosclerosis affect autonomic regulation of heart rate and circulation. Although diabetic autonomic neuropathy may act as a confounder and actually decrease the association of depressed HRV with mortality (Stein et al. 2004), other studies have shown that autonomic neuropathy, as reflected by impaired HRV, independently predicts post-AMI overall mortality in diabetic patients (Wheeler et al. 2002; Whang et al. 2003). Since untreated OSA increases sympathetic activation and is associated with hypertension, it can be expected to cause significant HRV alterations that could potentially be reversed with CPAP. More data are needed to confirm the independent predictive value of HRV alterations in an individual patient and in different disease states or pathophysiological conditions.

3. AIMS OF THE STUDY

This study aimed at finding clinical risk stratification tools for patients with PAD undergoing surgical revascularisation. To achieve this, prevalence and clinical significance of OSA were determined in consecutive patients that were referred to sub-inguinal vascular surgery due to lower limb ischaemia. In addition, characteristics of sleep-time HRV were measured. The specific objectives were as follows:

1. Determine the prevalence and clinical characteristics of OSA in the study population by performing a preoperative PSG to all enrolled patients.

2. Establish the predictive value of OSA for major postoperative adverse events following vascular surgery.

3. Assess the characteristics of HRV in patients with PAD in different sleep stages, compared to healthy controls, and the impact of HRV alterations on postoperative outcome

4. Explore the effect of OSA and its severity on cardiac autonomic regulation and HRV in the study subjects.

4. MATERIALS AND METHODS

4.1 Study design and subjects

The BAROSLEEP trial (ClinicalTrials.gov identifier NCT00712946) was designed to increase our understanding of the pathophysiology underpinning the poor long-term outcome of PAD patients. Between April 2006 and December 2011, consecutive patients aged 40 years or more and scheduled for elective sub-inguinal revascularisation in the Turku University Hospital Department of Vascular Surgery were asked to participate in the study and undergo preoperative polysomnography with HRV measurements. Types of vascular surgery included femoral cross-over, endarterectomy and femoro-popliteal bypass with autologous vein or prosthetic graft. Criteria for exclusion were pre-existing OSA syndrome, clinical heart failure, atrial fibrillation (HRV analysis requires sinus rhythm), non-cooperation (immobility, dementia or otherwise insufficient cognitive function), end-stage renal disease, coronary bypass within 3 years or other major surgery within 3 months prior to enrolment. Altogether, 301 patients were screened, 156 of which were excluded due to the criteria mentioned above. Of the 145 eligible patients 59 did not consent and were excluded. Of the 86 enrolled patients, two more had to be excluded due to PSG failure. Finally, 84 patients completed the follow-up; the flow chart detailing the screening and exclusion of patients according to each criterion is shown in Figure 1. In addition, a control group was recruited (by an in-hospital advertisement) from 22 healthy volunteers without hypertension, diabetes or any cardiovascular disease. The study was approved by the Ethics Committee of the Hospital District of Southwest Finland, Turku, Finland (statement and approval number 404/2005) and subjects willing to participate signed a written informed consent. Postoperative follow-up was planned to continue until at least one year had passed from the surgery of the last recruited patient.

4.2 Data collection and analysis

4.2.1 Clinical evaluation

The enrolled patients underwent a detailed clinical evaluation. Medical history was taken; coronary artery disease and hypertension were considered to be present if previously diagnosed, i.e. no specific diagnostic tests were made for these. Echocardiography was performed routinely; patients with a mildly decreased LVEF (40-50%) but without clinical heart failure were not excluded. The 2-hour glucose tolerance test was done for those without pre-existing diabetes mellitus and the diagnosis of diabetes, impaired fasting glucose or impaired glucose tolerance was made according to the current criteria (American Diabetes Association 2015). Venous blood samples were taken to determine lipid profile (unless available from

hospital records). Waist circumference was also measured (increased when ≥88 cm in females, ≥103 cm in males) and used together with hypertension, impaired glucose metabolism, decreased HDL (<1.03 mmol/l in males, <1.3 mmol/l in females) or elevated triglycerides (≥1.7 mmol/l) to diagnose metabolic syndrome, i.e. if three more of the above criteria were met (Grundy et al. 2005). ABI and toe pressures were measured to assess lower limb circulation; the latter was used in diabetic patients with unreliably high ABI due to mediasclerosis.

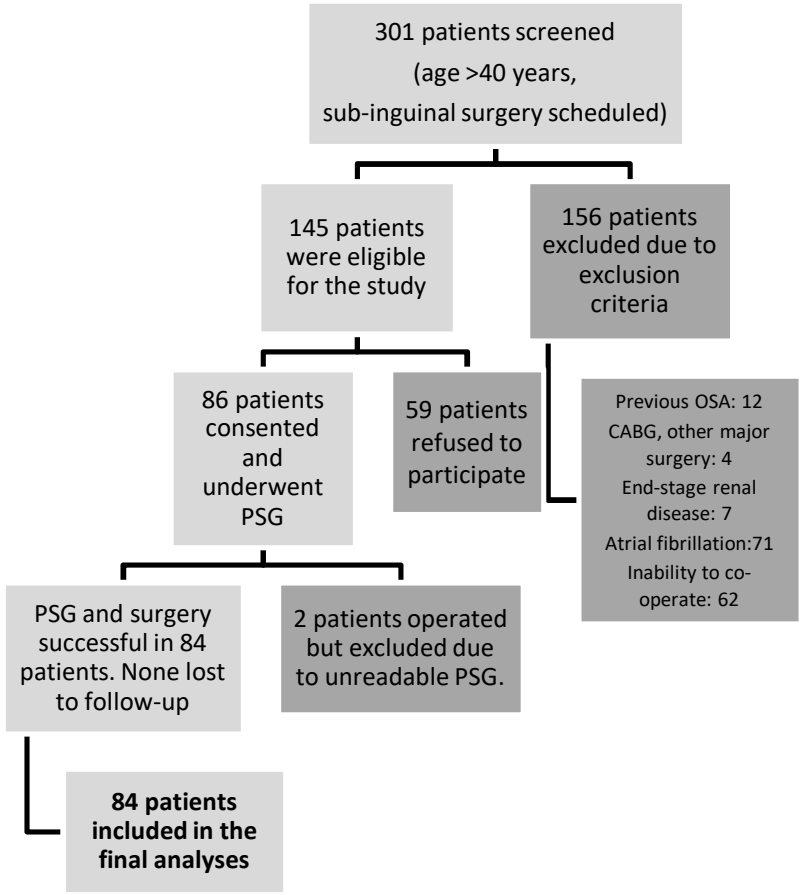

Figure 1. Patient recruitment from screening to endpoint analysis. CABG = Coronary artery bypass grafting, Inability to co-operate = immobility, dementia or otherwise insufficient cognitive function, OSA = Obstructive sleep apnoea, PSG = Polysomnography. (Modified from original publication II)

4.2.2 Sleep studies

4.2.2.1 PSG recordings and analyses

An overnight PSG (Embla/Somnologica 3.0; MedCare, Reykjavik, Iceland) was performed preoperatively for all the included patients and healthy controls. The PSG setting included four EEG channels, two EOG channels, EMG and ECG. Respiratory flow was measured with a nasal cannula connected to a pressure transducer. Two pulse oximeters were used, one to record arterial oxyhaemoglobin saturation and another for plethysmographic pulse wave. The PSG recordings were analysed immediately before the investigators had any knowledge of possible adverse events. Sleep stages were scored according to the standard rules for sleep scoring (Rechtschaffen & Kales 1968) and arousals from sleep were identified using appropriate guidelines (Sleep Disorders Atlas Task Force of the American Sleep Disorders Association 1992). A cessation of breathing for at least ten seconds was required to score an apnoea and the definition of hypopnoea was a tidal volume reduction of >50% combined with oxyhaemoglobin desaturation ≥4% (both required). The AHI was calculated and the oxyhaemoglobin desaturation index (ODI) was also determined as the number of desaturations (≥4%) per hour of sleep (American Academy of Sleep Medicine Task Force 1999). The ODI was used instead of the AHI to diagnose OSA in patients with unanalysable respiratory flow due to detached nasal cannula. Arousal index was determined as the number of arousals per hour of sleep. PTT was calculated from the R-peak of the ECG to the peak of the peripheral pulse wave; the same device was used to monitor both the ECG and plethysmography. The respiratory swing observed in the PTT was displayed graphically by the analysis software (WinCPRS 1.1.6.0 for Windows; Absolute Aliens Inc., Turku, Finland) and used to differentiate obstructive and central apnoea from each other (each apnoea analysed separately on the PTT timeline), as described in detail elsewhere (Argod et al. 1998; Argod et al. 2000).

4.2.2.2 Classification of OSA severity

The different classifications of OSA severity that were used in the sub-studies are summarised here and the corresponding original publication is referred to with its Roman numeral.

I. For the first study determining the prevalence and characteristics of OSA in patients with PAD, OSA was diagnosed with an AHI ≥5/hour and its severity was graded as mild (AHI 5-15/hour), moderate (AHI 15-30/hour) or severe (≥30/hour) as is the common classification in clinical use (American Academy of Sleep Medicine Task Force 1999).

II. In the second study assessing the association of OSA with postoperative adverse events, a dichotomic threshold of AHI ≥20/hour indicating significant OSA was used. This was based both on previous literature (Martínez-García et al. 2009; Gooneratne et al. 2011) and statistical

analyses performed with this study population. Preliminary analyses were first performed with increments in the AHI of 10/hour, i.e. the study sample was divided into patients with AHI 0–10/hour, 10–20/hour, 20–30/hour and >30/hour. The latter three groups were then compared to the first. With the first two categories appearing insignificant and the last two the most likely predictors of adverse events in terms of hazard ratio (see Results section for details), these pairs of patient groups were combined to determine the AHI≥20/hour as cut-off.

III. In the third study dealing with the effect of HRV on postoperative outcome, the same dichotomic cut-off was first used. This was done partly to simplify the analysis but also to elucidate the pathophysiology association of OSA with adverse outcome, i.e. to determine whether OSA *per se* (with the same threshold) is associated with decreased HRV and impaired autonomic control of heart rate. Furthermore, to evaluate the evolution of the different HRV parameters as the AHI and severity of OSA progress, the study population was also divided into subclasses with equal increments in the AHI with steps of 10 events/hour (i.e. AHI 0–10/hour, 10–20/hour, 20–30/hour and >30/hour).

4.2.2.3 Sleep questionnaires

Sleep history was taken; both the Epworth Sleepiness Scale (ESS) and the Berlin Questionnaire (BQ) were performed to assess EDS, snoring and other symptoms of OSA. An ESS score of ≥10 indicated EDS (Johns 1991) and two or three positive categories in the BQ showed a strong suspicion of OSA (Netzer et al. 1999). EDS was handled also as a categorical variable, in addition to the ESS score. If OSA was diagnosed in the PSG, scores from the questionnaires were reviewed and the study subjects were offered the possibility to be referred to a pulmonologist for consideration of CPAP therapy. The surveillance of the outcome of these consultations was not included in the follow-up protocol.

4.3 HRV analysis

4.3.1 Acquisition, reviewing and editing of ECG data

The ECG data was transferred from a Datex-Ohmeda scanner to a laptop computer and the files were converted to be readable with the analysis software (WinCPRS; Absolute Aliens Inc., Turku, Finland) HRV was analysed during continuing sleep in 10-minute epochs; the sleep stage without awakenings was required. HRV was also analysed during 10-minute wake periods in the evening and in the morning, separately. The ECG was then carefully reviewed and epochs with ectopic beats more than 10 % were excluded. All other ectopic beats were interpolated, i.e. the extrasystolias were removed and replaced in the exact middle of the preceding and following sinus beats. This method has been used earlier and is considered reliable

when less than 10 % of total beats are interpolated (Huikuri et al. 1996). The stationarity of the data was tested with the StatAvF algorithm of the analysis software (see supplementary files in original publication III for details).

4.3.2 HRV parameters

NNI between normal (or interpolated) R-peaks of the QRS complex of the ECG was used to analyse HRV parameters in the time and frequency domain. The statistical time domain measurements that were performed included standard deviation of NNI, root mean square of the sum of successive differences (RMSSD) between adjacent NNI (i.e. beat-to-beat variability) and proportion of NNI >50 ms (pNN50). The frequency domain measurements included ULF, VLF, LF and HF power as well as the LF/HF ratio. The normalised units of LF and HF (nLF and nHF, respectively) were also measured. Of the non-linear measurements, sample entropy was calculated and fractal characteristics of the NNI time series were measured using the scaling exponent alpha 1 determined by DFA (see 2.6.2.2 in Review of the Literature).

4.4 Follow-up and definition of outcome

After the operation, the patients were followed at the surgical ward and cardiac troponin T (cTn-T) was routinely measured on three consecutive postoperative days. Any elevation of cTn-T over the threshold of 0.03 mg/ml indicated postoperative AMI. After hospital discharge, the patients were routinely seen by a surgeon and one of the investigators at the surgical outpatient ward six weeks and one year postoperatively. Later, the patients were contacted by phone at least once per year. Information of adverse events were obtained by interviewing the patients and further details were acquired from their medical records. In terms of long-term outcome, MACCE was used as a combined endpoint. MACCE included cardiac death, AMI, any need for coronary revascularisation (CABG or coronary angioplasty, excluding elective angiography not ending in angioplasty), unstable angina pectoris requiring hospitalisation and stroke (ischaemic or haemorrhagic). AMI was determined by the third universal definition (Thygesen et al. 2012).

4.5 Statistical analysis

4.5.1 Calculation of sample size

Based on a pre-study power analysis, the original intention was to recruit a total of 100 patients in order to evaluate the possible preoperative predictive value of altered short-term fractal heart rate variability (i.e. scaling exponent alpha 1) in different sleep stages for postoperative MACCE in PAD patients. According to earlier studies approximately one third and up to 50% of PAD patients should develop a myocardial infarction (i.e. cTn-T $\geq$0.03 mg/ml, the detection threshold when the study

procedures were carried out) within three postoperative days and the five-year mortality in these patients was expected to be approximately 30 % (Conte et al. 2001; Landesberg et al. 2003; Levy et al. 2011). Power was fixed to 85 % and significance level to 0.05 in the calculations. The calculated total number of patients varied between 80 and 100, depending on the incidence of myocardial infarction between 30-50 % to reveal statistically significant differences. Mainly due to exclusion criteria and a large number of patients not consenting, the enrolment was difficult and slow. Therefore, it was decided to stop recruitment and perform survival analysis after the 86th patient had gone through a follow-up of at least one year.

4.5.2 Probability of OSA

After OSA was diagnosed and classified, the confidence interval of its prevalence was determined by binomial distribution. Spearman's correlation coefficient was used to test for the interdependence of the AHI and ODI in this study population. The association of each baseline clinical characteristic (smoking status, metabolic syndrome, BMI, waist circumference, diabetes, hypertension, coronary artery disease, stroke history, LVEF, LDL, HDL, HDL/cholesterol ratio, triglycerides, ABI, toe pressure, PAD duration, critical ischaemia) and sleep variable (BQ and ESS score, EDS, arousal index, mean and lowest nocturnal oxyhaemoglobin saturation, cumulative time below 90 % saturation) with the severity of OSA was tested using cumulative logistic regression models. Because the study sample had few patients having no OSA at all, the association of the predictors with the prevalence of OSA in general was not tested separately. Instead, the severity of OSA (including patients with no OSA) was used as an ordinal dependent variable. After excluding variables with a significance of association of $P > 0.1$, the independent predictive value of each remaining variable was determined using a stepwise multivariate analysis, adjusted for age and gender. The cumulative odds ratio (OR) with 95 % confidence interval (CI) predicting the worsening of OSA and corresponding to a change equal to the standard deviation of each predictor was then calculated.

4.5.3 OSA and other predictors of MACCE

The preliminary analyses were performed as described in section 4.2.2.2, item II. Due to sample size, very similar hazard ratios and confidence intervals it was deemed viable to combine the groups with AHI 20-30 and AHI >30. That being said, the AHI ≥20 threshold for significant OSA was determined as a post hoc decision based both on previous literature and observations made in this study. A Kaplan–Meier plot was then used to show the impact of significant OSA on event-free survival. Two-tailed P-values of <0.05 were considered statistically significant.

Univariate Cox regression analysis was used first to determine variables associated with MACCE. All clinical variables recorded at baseline were tested separately (age, gender, smoking status, PAD duration, stroke history, coronary artery disease, metabolic syndrome, diabetes, hypertension, critical ischaemia, ABI, BMI, waist

circumference, LVEF, lipid values). Of the sleep variables, significant OSA (AHI ≥20/hour), central sleep apnoea, arousal index, mean (SaO_2 Mean) and lowest (SaO_2 Nadir) oxygen saturation, time below 90% saturation (SaO_2 T90), ESS score and pathological BQ score as a cathegorical variable were tested. In these analyses, the duration of PAD history was used as a categorical variable (0–3 years and ≥4 years, see below for details). ODI was excluded from the final regression model because of its close dependence of the AHI (and was also used to define hypopnoea) to avoid the multicollinearity problem that would undo the default assumptions of the multivariate analysis (see Results section for details). Variables significantly associated with the occurrence of MACCE in the univariate analysis were included in a multivariate Cox regression analysis using a stepwise selection method (inclusion criteria $P < 0.05$ and exclusion criteria $P \geq 0.05$). The proportional hazards assumption in Cox models was tested with Martingale Residuals and graphically using the plots of the logarithm of the negative logarithm (log(-log(S)) of the estimated survival function against survival time; the proportional hazards assumptions were met. The results are presented using hazard ratio (HR) with 95% CI.

In the regression models, the duration of PAD was divided into subclasses and handled as a categorical variable as follows:

1. PAD_year2, 1 = 0−1 years, 2 = 2−16 years
2. PAD_year3, 1 = 0−2 years, 2 = 3−16 years
3. PAD_year4, 1 = 0−3 years, 2 = 4−16 years
4. PAD_year5, 1 = 0−4 years, 2 = 5−16 years

Of these, the last three (*i.e.* PAD duration of <3 years, <4 years or <5 years) were significant predictors (but not <2 years). The four-year cut-off for PAD duration was finally chosen because it had the most significant P-value and highest hazard ratio (P=0.030, HR 3.32, 95% CI 1.13–9.79) in the univariate analysis, compared to the alternatives. This threshold was also deemed clinically relevant.

4.5.4 Associations of HRV alterations with OSA and MACCE

The HRV parameters were analysed from 1–5 different 10-minute epochs (per subject) of S2 sleep, 1–3 epochs of REM sleep and 1–2 epochs of S3-4 sleep. Results obtained from the same sleep stage were then averaged. Wakefulness periods in the evening and in the morning after awakening were analysed separately; these results were not averaged. Finally, analyses with all sleep stages (S2, S3-4, REM) combined were performed from 1–7 averaged epochs (per study subject, some of which had only one analysable 10-minute sample from one sleep stage).

One-way analysis of variances (ANOVA) was used to test for differences in parameters. Non-normally distributed variables were log-transformed (natural logarithm) and the requirement for normal distribution was met after the transformation. Dunnett's post hoc adjustment for multiple comparisons was used in

the ANOVA model. An analysis of covariances (ANCOVA) adjusted for age, body mass index, coronary artery disease and PAD history of <4 years was then performed to test for an independent association of significant OSA (AHI ≥20/hour) and MACCE (healthy controls not included) with each HRV parameter. In the analyses with all sleep stages combined, ANOVA and ANCOVA models were also used to test for independent association of the HRV parameters with worsening OSA (AHI 10-20/hour, AHI 20-30/hour and AHI >30/hour with AHI <10/hour used as a control group) and MACCE.

4.5.5 Other statistical procedures

In the analyses regarding the effect of significant OSA (AHI ≥20/hour) on the incidence of MACCE, the statistical differences in each clinical (demographics, prevalence of co-morbidities, ABI and LVEF) and sleep variable (ESS and BQ scores, prevalence of EDS, PSG parameters) between patients with and without significant OSA were determined using the Mann–Whitney U-test for continuous variables and Fisher's exact test for categorical variables. The Shapiro–Wilk test was used to test for normal distribution of data.

In the HRV analyses, patient groups with and without MACCE, and patients with and without significant OSA (AHI >20/hour) were compared to healthy controls with ANOVA for normally distributed variables; Dunnett's post hoc correction was used to adjust for multiple comparisons. Again, non-normally distributed variables were log-transformed before any of these analyses were performed; Kruskal-Wallis's test and Mann-Whitney's U-test with Bonferroni's adjustment for multiple comparisons were used to test for differences in variables that were still skewed after log-transformation. Exact Fisher's test was used to test for differences in categorical variables between patient groups. P-values below 0.05 were considered statistically significant. In the tabular presentation, data is described using mean (standard deviation, SD) for normally distributed variables and median [interquartile range, IQR] for non-normally distributed variables.

5. RESULTS

5.1 Patient demographics and clinical characteristics

All of the included 84 subjects (62 % male, aged 67 ± 9 years) were outpatients, living independently and some of them were still working actively. The average duration of PAD from diagnosis to enrolment was approximately four years and 31 patients (37 %) had PAD history longer than four years and the mean ABI was 0.55. Besides PAD, the majority had other manifestations or risk factors of cardiovascular such as coronary artery disease (37 %), stroke history (17 %), diabetes (43 %) or hypertension (83 %). While obesity was in a minority as 14 patients (17 %) had a BMI of 30 kg/m^2 or greater (average BMI 26 kg/m^2), especially female patients had an elevated waist circumference (males 101 ± 9 cm, females 102 ± 12 cm) and metabolic syndrome was diagnosed in 51 (61 %) patients. LVEF decreased significantly in parallel with worsening OSA despite remaining in the normal range; only four patients had a slightly abnormal systolic function (LVEF 40-50 %) without clinical heart failure. There was no difference between patient groups (according to severity of OSA or incidence of MACCE) in the usage of beta-blockers or other pertinent long-term medications (antihypertensives, antithrombotic agents, opioids, benzodiazepines). Antihypertensive medication was used by 91 % and 23 % had three or more antihypertensives. Acetylsalicylic acid was used by 83 % and 62 % were on statins.

The demographic features and baseline clinical characteristics of patients participating in the study are summarised in Table 1. Subjects that were otherwise eligible but refused their consent were significantly older than those who were enrolled and completed the follow-up (71 vs. 67 years; P = 0.02). These two groups did not differ in any other clinical characteristics that were available from those refusing to participate (gender, smoking status, BMI, diabetes, hypertension, CAD, stroke history, ABI, PAD duration, presence of critical ischaemia).

5.2 Demographic and clinical characteristics of controls

One control subject had to be excluded due to failed PSG. Of the remaining 21 controls, there were three subjects with mild OSA, three with moderate OSA and three with severe OSA. Thus, the prevalence of OSA in this supposedly healthy group was 43 %. It was decided to include the three subjects with mild OSA (having the AHI in the range of 5 – 9/hour) and to exclude the ones with moderate or severe OSA due to the potiential effect of OSA on HRV. Thus, 15 controls were included in the HRV analyses. The enrolled patients were older than the control subjects (67 vs. 63 years; P = 0.049). There was also a higher BMI (27 vs. 24 kg/m^2; P = 0.0004), lower LVEF (63 % vs. 70 %; P = 0.006) and more common male gender (67 vs. 33 %; P = 0.0496) among the included patients than controls.

Table 1. Baseline characteristics according to severity of obstructive sleep apnoea (OSA).

	All patients n = 84	No OSA n = 12	Mild OSA n = 25	Moderate OSA n = 23	Severe OSA n = 24
Age, years	67 (9)	65 (7)	65 (10)	69 (8)	70 (8)
Male, n	52 (62)	7 (58)	11 (44)	14 (61)	20 (83) *
Smoker, n	32 (38)	7 (58)	12 (48)	5 (22)	8 (33)
Metabolic sdr., n	51 (61)	5 (42)	14 (56)	15 (65)	17 (71)
BMI, kg/m^2	27 (4)	27 (3)	27 (4)	26 (5)	28 (4)
Waist circumference, cm					
Male	101 (9)	102 (6)	98 (11)	102 (12)	101 (6)
Female	102 (12)	105 (16)	105 (11)	97 (12)	98 (15)
Diabetes, n	36 (43)	6 (50)	12 (48)	11 (48)	7 (29)
Hypertension, n	64 (76)	8 (67)	16 (64)	20 (87)	20 (83)
CAD, n	31 (37)	3 (25)	8 (32)	11 (48)	9 (38)
Stroke, n	9 (11)	4 (33)	2 (8)	1 (4)	2 (8)
LVEF, %	63 (8)	68 (5)	66 (7)	63 (8)	59 (9) ‡
Cholesterol, mmol/L	4.3 (1.0)	4.3 (1.2)	4.3 (0.9)	4.5 (1.0)	4.3 (1.1)
LDL, mmol/L	2.2 (0.8)	2.1 (0.9)	2.0 (0.8)	2.3 (0.5)	2.2 (1.0)
HDL/Chol, %	34 (10)	37 (13)	38 (9)	31 (8)	32 (10) †
TGL, mmol/L	1.4 [1.2]	1.0 [1.2]	1.4 [1.0]	1.6 [1.2]	1.5 [1.3]
ABI, ratio	0.6 (0.2)	0.5 (0.2)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)
Toe pressure, mmHg	51 (24)	44 (25)	56 (16)	49 (16)	52 (32)
PAD history, years	2 [5]	2 [5]	3 [4]	4 [6]	4 [6]
Critical ischaemia, n	11 (13)	4 (33)	1 (4)	2 (9)	4 (17)

Data are number (percentage) of patients, mean (standard deviation) or median [interquartile range]. ABI = Ankle-brachial index, BMI = Body mass index, CAD = Coronary artery disease, HDL/Chol = High density lipoprotein/Total cholesterol ratio, LDL = Low density lipoprotein, LVEF = Left ventricular ejection fraction, Metabolic sdr. = Metabolic syndrome. PAD history = Time from the onset of peripheral arterial disease, TGL = Triglycerides. The significance of association with the severity of OSA was tested with univariate cumulative logistic regression analysis (analysed with n = 82 for original publication I); p-values reflect the association of the variable with the severity of OSA. *: p = 0.02; †: p = 0.03; ‡: p = 0.002. (Modified from original publication I)

5.3 Prevalence and clinical characteristics of OSA

OSA of any severity (AHI ≥5/hour) was detected in 72 out of 84 patients (overall prevalence of 86 %; 95 % CI 76 – 92 %). In the whole study population, 25 (30 %) had mild OSA (AHI 5 - 15/hour), 23 (27 %) had moderate OSA (AHI 15 - 30/min) and 24 (29 %) had severe OSA (AHI ≥30/hour). In other words, OSA was moderate or severe in over one half of all patients and in approximately two thirds of the patients with OSA. Baseline clinical characteristics according to this classification of OSA severity are shown in Table 1. ODI (mean 23/hour, median 17/hour, IQR 26) correlated very closely with the AHI (mean 23/hour, median 18/hour, IQR 26) in the whole study population (Spearman's correlation coefficient r=0.93). The type of apnoea was predominantly obstructive despite a relatively high percentage of central episodes (mean 19 %, median 22 %, IQR 13) but the central apnoea index (mean 5/hour, median 4/hour, IQR 5) in the whole study population was low. The proportion of central apnoea did not differ between patients using opioids at baseline compared to those who did not (21 % vs. 23 %).

As expected, the arousal index and SaO_2 T90 increased with worsening OSA. SaO_2 Nadir was also worst in patients with severe OSA but there was no difference in SaO_2 Mean across the OSA severity categories. The sleep variables are summarised in Table 2.

In general, the patients diagnosed with OSA in this study were either minimally symptomatic or completely asymptomatic, i.e. they did not suffer from sleepiness. The ESS scores were low as a whole (mean 5, median 4, total range 0 – 17) and did not increase with worsening OSA; EDS (ESS score > 10) was evident in a total of eight patients (11 % of all patients with OSA), five of which had only mild OSA while there were two patients with moderate OSA and one with no OSA. Notably, none of the patients with severe OSA had EDS. Snoring was still common along with general fatigue (but without excessive sleepiness) which was observed in the BQ scores. Two or more positive BQ categories seemed to be more common in patients with OSA than in those without and especially in moderate or severe OSA but the difference was not significant.

5.3.1 Variables associated with the presence and severity of OSA

In the cumulative logistic regression analysis (performed with the 82 patients that were included in original publication I), LVEF and HDL/Chol, SaO_2 Nadir and arousal index along with male gender and age were the only variables associated with the severity of OSA. The presence or severity of OSA was not related to obesity, metabolic syndrome or diabetes. Hypertension seemed to be more prevalent in patients with moderate or severe OSA but the difference did not reach statistical significance. The AHI did not correlate to the severity of atherosclerosis in terms of ABI and toe pressures or presence of other cardiovascular manifestations (coronary artery disease, stroke history). Arousal index, SaO_2 Nadir and SaO_2 T90 saturation excluded were considered inherently associated with OSA and were thus excluded

from the multivariate model. In the multivariate analysis adjusted with age and gender, LVEF (cumulative OR 2.3, 95% CI 1.4 – 3.8; P = 0.002, corresponding to a decrease equal to SD of 8 %-point) and HDL/Chol (cumulative odds ratio 1.7, 95% CI 1.1 – 2.7; P = 0.03, corresponding to a decrease equal to SD of 10 %-point) remained significantly associated with the severity of OSA. Decreasing percentages in both parameters were associated with worsening OSA so that the OR values reflect the odds of a patient having more severe OSA compared to lower OSA categories (no OSA handled as one of the categories).

Table 2. Sleep variables and sleep times according to the severity of OSA

	No OSA n = 12	Mild OSA n = 25	Moderate OSA n = 23	Severe OSA n = 24
BQ 2-3, n	4 (33)	10 (40)	12 (52)	11 (46)
ESS score, range	5 (1-12)	6 (0-17)	6 (0-11)	4 (0-10)
EDS (ESS >10), n	1 (8)	5 (20)	2 (9)	0 (0)
Arousal index, 1/h	13 (7)	17 (9)	22 (9) *	27 (9) ‡
CSA, %	23 (12)	22 (11)	23 (6)	24 (8)
SaO_2 Nadir, %	88 (3)	85 (5)	83 (6) *	81 [14] †
SaO_2 Mean, %	93 (2)	93 (2)	95 [3]	94 [4]
SaO_2 T90, minutes	0 [4]	3 [12]	4 [9]	14 [97] *
TST, minutes	293 (80)	327 (83)	269 (80)	261 (87)
S1 sleep, minutes	32 (22)	36 (20)	46 (30)	66 (31)
S2 sleep, minutes	184 (60)	214 (62)	165 (61)	143 (66)
S3-4 sleep, minutes	34 (23)	26 (32)	24 (25)	21 (20)
REM sleep, minutes	42 (25)	50 (35)	34 (19)	31 (29)

Data are number (percentage) of patients, mean (standard deviation) or median [interquartile range] unless otherwise stated. BQ 2-3 = 2 or 3 positive Berlin Questionnaire categories indicating high risk of OSA, CSA = Central sleep apnoea percentage, EDS = Excessive daytime sleepiness, ESS = Epworth sleepiness scale, REM = Rapid eye movement, SaO2 Mean = Average oxyhaemoglobin saturation, SaO2 Nadir = Lowest oxyhaemoglobin saturation, SaO2 T90 = Cumulative time below 90% oxyhaemoglobin saturation. The significance of association with the severity of OSA was tested with univariate cumulative logistic regression analysis (analysed with n = 82 for original publication I, sleep times not included); p-values reflect the association of the variable with the severity of OSA. *: p = 0.02; †: p = 0.0001; ‡: p < 0.0001. (Modified from original publication I)

5.4 Endpoints during follow-up

After a median follow-up of 52 months (ranging from 14 to 84 months), eighteen patients had died (all-cause mortality 21 %). Nine of these were cardiac deaths, two were fatal cerebrovascular events (one ischaemic and one haemorrhagic stroke), and seven were due to other causes (cancer, septicaemia, liver cirrhosis, pulmonary fibrosis, alcoholism). Altogether, 23 patients suffered a MACCE and the first event of each patient occurred after a median of 16 months (ranging from 0 to 75 months) after the index surgery. Of short-term events, one AMI and one cardiac death occurred within thirty days after the surgery in addition to one perioperative myocardial infarction (elevated cTn-T) within three days after surgery. Altogether, seven events and three deaths took place within the first postoperative year (one-year mortality 4 %). One-year mortality for significant OSA was 8 % and all patients dying within one year had AHI ≥20/hour. A summary of all endpoints, including limb complications (e.g. graft occlusion, amputation) is shown in table 3.

After a follow-up of five years (no regression analysis performed), 21 patients had died (of any cause), yielding a five-year mortality of 25 %. Of these, 14 had significant OSA (five-year mortality 36 % in patients with AHI ≥20/hour vs. 8 % in those without).

Table 3. Major endpoints according to severity of obstructive sleep apnoea.

	All patients n = 84	AHI <20 n = 45	AHI ≥20 n = 39
All-cause mortality, n	18 (21)	6 (13)	12 (31)
Combined MACCE, n	23 (27)	6 (13)	17 (44) †
Fatal MACCE, n	11 (13)	2 (4)	9 (23) *
Cardiac death, n	9 (11)	1 (2)	8 (18) *
Stroke, n	2 (2)	1 (2)	1 (2)
Non-fatal AMI, n	7 (8)	2 (4)	5 (13)
Coronary revascularisation, n	4 (5)	2 (4)	2 (5)
Unstable angina pectoris (hospitalisation), n	1 (1)	0 (0)	1 (3)
Limb complication, n	22 (26)	10 (22)	12 (31)
Amputation, n	3 (4)	0 (0)	3 (8)
Assisted patency (PTA included), n	19 (23)	10 (22)	9 (23)

Data are number (percentage) of patients. AMI = Acute myocardial infarction, MACCE = Major adverse cardiovascular or cerebrovascular event, PTA = Percutaneous transluminal angioplasty. P-values were calculated using univariate Cox regression analysis. *: $P < 0.05$, †: $P < 0.01$ (between patients with and without AHI ≥20/hour) (Reproduced from original publication II)

5.5 Predictors of MACCE

In the univariate Cox regression, three different categories of PAD duration (*i.e.* <3 years, <4 years or <5 years) were significant predictors (but not <2 years). The four-year threshold for PAD duration had the most significant P-value and highest hazard ratio (P = 0.03, HR 3.32, 95% CI 1.13 – 9.79) in the univariate analysis, compared to the alternatives and was chosen as threshold (see Materials and Methods 4.5.3). AHI was significantly higher in patients suffering a MACCE (P = 0.049). Other significant predictors were age (P = 0.03), pre-existing coronary artery disease (P = 0.004), PAD history of <4 years (as above), SaO_2 Nadir (P = 0.03), HDL (P = 0.04) and HDL/Chol (P = 0.02). In the analyses to determine a threshold in the AHI (see Materials and Methods 4.2.2.2), AHI 20-30 (HR 3.0, 95% CI 0.9 - 10.5, P = 0.08) and AHI >30 (HR 3.4, 95% CI 1.0 - 11.3, P = 0.04) appeared as the best predictors of MACCE with other significant factors included; the AHI 0-10/hour and AHI 10-20/hour seemed to be insignificant. When the cut-off of AHI ≥20/hour was chosen, it appeared as the most significant predictor of MACCE (P = 0.003).

Variables that were shown to be significant predictors of MACCE in the univariate analysis were included in the multivariate Cox regression model. ODI was left out of the regression analyses to avoid multicollinearity because of its close associaton with the AHI. In addition, SaO_2 Nadir and HDL were excluded as inherently related to significant OSA and HDL/Chol, respectively (HDL/Chol chosen over HDL as the more significant predictor). AHI ≥20/hour (HR 5.1, 95% CI 1.9 – 13.9; P = 0.001) and pre-existing coronary artery disease (HR 4.4, 95% CI 1.8 – 10.6; P = 0.001) remained as strong independent predictors. PAD history of <4 years (HR 3.8, 95% CI 1.3 – 11.5); P = 0.02) and HDL/Chol (HR 0.95 per 1% increase 95% CI 0.90 – 1.00; P = 0.048) also predicted MACCE. To test the usefulness of ODI alone, a multivariate analysis was also done with the AHI replaced by the ODI. With the corresponding cut-off, ODI ≥20/hour was also an independent predictor of MACCE (HR 7.0, 95% CI 2.4 - 20.4, p=0.0004). Coronary artery disease, PAD history ≤4 years and HDL/Chol ratio also remained significant with similar P-values and confidence intervals.

A Kaplan-Meier plot visualising the effect of significant OSA (AHI ≥20/hour) on event-free survival is shown in Figure 2. None of the pertinent medications, including beta-blockers, had a significant association with outcome. All factors that significantly influenced the occurrence of MACCE in the univariate or multivariate analyses are summarised in table 4.

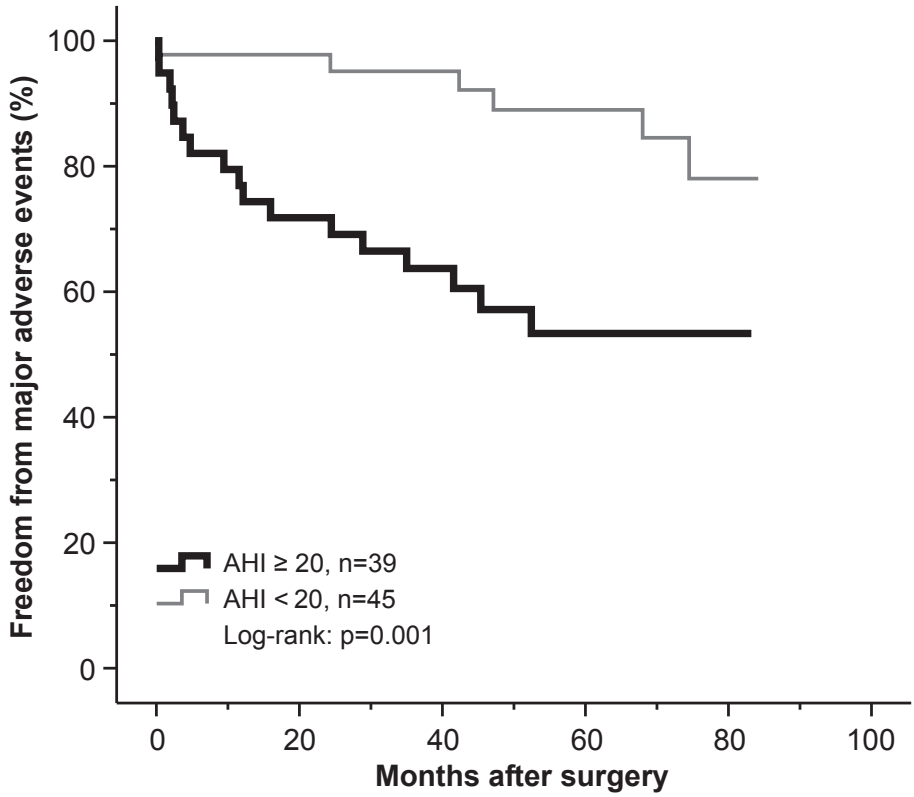

Figure 2. Survival plot for freedom from major adverse cardiovascular and cerebrovascular events according to severity of obstructive sleep apnoea based on the threshold of ≥20/hour in the apnoea-hypopnoea index (AHI). (Modified from original publication II)

Table 4. Univariate and multivariate predictors of MACCE

	Univariate analysis		Multivariate analysis	
Predictor	***HR (95 % CI)***	***P***	***HR (95 % CI)***	***P***
Age (per each year)	1.06 (1.01 – 1.11)	0.028	NS	
SaO_2 Nadir (per each %)	0.94 (0.89 – 0.99)	0.029	NS	
Coronary artery disease	3.50 (1.51 – 8.10)	0.004	4.37 (1.81 – 10.6)	0.001
PAD history <4 years	3.32 (1.13 – 9.79)	0.030	3.80 (1.26 – 11.5)	0.018
HDL/Chol (per each %)	0.94 (0.90 – 0.99)	0.021	0.95 (0.90 – 1.00)	0.048
AHI ≥20/hour	4.26 (1.66 – 10.9)	0.003	5.13 (1.89 – 13.9)	0.001

AHI = Apnoea/hypopnoea index, CI = Confidence interval, HDL/Chol = High density lipoprotein/Total cholesterol ratio, HR = Hazard ratio, PAD = Peripheral arterial disease. SaO2 Nadir = Lowest sleep-time oxyhaemoglobin saturation. NS = Not selected into the final model. Multivariate analysis was done using stepwise selection method (inclusion criteria $p < 0.05$ and exclusion criteria $p \geq 0.05$). (Reproduced from original publication II)

5.6 Results of the HRV analyses

5.6.1 Characteristics of patients and controls

ECG data eligible for HRV analysis was available from a total of 75 patients (71 in S2 sleep, 31 in S3-4 sleep, 58 in REM sleep, 68 in evening wake and 60 in morning wake). One patient had analysable ECG only during wakefulness; thus, HRV during sleep was available from 74 patients. In other patients, the ECG had excessive ectopic beats or was otherwise too disturbed by artefacts. Of the 75 patients, 64 (85 %) had at least mild OSA and 36 (48 %) had OSA with AHI ≥20/hour. In terms of outcome, 22 (29 %) of them suffered a MACCE during the follow-up and 17 (23 %) patients died. All of the 15 included controls had analysable ECG data in S2 sleep, evening wake and morning wake; nine had data available in S3-4 sleep and 14 in REM sleep. The age difference was not significant (67 vs. 63 years; $p = 0.08$) between the patients eligible for the HRV analysis and the included controls (the controls were only used as a reference group in the HRV studies). Likewise compared, there remained a significantly higher BMI (27 vs. 24 kg/m^2; $p = 0.009$), lower LVEF (64 % vs. 70 %; $p=0.01$) and more common male gender (67 vs. 33 %; $p = 0.02$) among the included patients than in the controls.

In the StatAvF stationarity testing, 6 % of the epochs chosen for analysis (patients and controls combined) were non-stationary (4 % in S2 sleep, 2 % in S3-4 sleep, 9 % in REM sleep and morning wake, 10 % in evening wake). Thus, most of the data were at least moderately stationary; 50 % of all the analysed epochs were considered fully stationary (66 % in S2 sleep, 81 % in S3-4 sleep, 38 % in REM sleep, 29 % in evening wake and 32 % in morning wake). The amount of fully stationary epochs in the included patients was very similar to that of the controls but the controls had even less nonstationary segments in all sleep stages and during wakefulness.

Because of its great significance in predicting adverse outcome, the same cut-off for significant OSA (AHI ≥20/hour) was applied to the HRV analyses. The purpose of this was to search for possible underlying factors that could explain the said association, i.e. whether significant OSA in patients with severe PAD is characterised by impaired ANS function and pathological HRV (e.g. sympathetic activation and loss of fractal heart rate control). Significant differences between PAD patients with and without AHI ≥20/hour, as well as with and without MACCE, to compared healthy controls are summarised below. For detailed tabular data of each HRV parameter in different stages of sleep and wakefulness, please see original publication III.

5.6.2 Comparisons between patients and controls

5.6.2.1 Time domain measures

In general, time domain measures of HRV showed few differences when patient groups (with and without AHI ≥20/hour, with and without MACCE) were compared

to controls. No differences in any of the time domain parameters were observed during evening wakefulness or S3-4 sleep. In the morning, NNI standard deviation was lower in patients with AHI ≥20/hour (37 ms vs. 52 ms; P = 0.02 and in those who suffered a MACCE (34 ms vs. 52 ms; P = 0.02) than in controls. Maximum heart rate during S2 sleep was higher (i.e. lower minimum NNI) in patients with AHI ≥20/hour (72/min vs. 65/min; P = 0.04). Those suffering a MACCE had a higher mean (67/min vs. 58/min; P = 0.02) heart rate during REM sleep.

5.6.2.2 Frequency domain measures in different sleep stages

In the frequency domain analyses, LF power was consistently lower in PAD patients than in controls. Conversely, HF power was higher in patients than in controls in S2, S3-4 and REM sleep as well as during morning wakefulness, except in those who suffered a MACCE. In the evening, all patient groups had lower HF power than controls. Consequently, the LF/HF ratio was significantly lower in all patient groups vs. controls, which was most clearly seen during S2 and REM sleep. None of the differences in HF power reached statistical significance but HF was mostly higher in all patient groups and in all sleep stages as well as during evening and morning wakefulness when measured in normalised units (except during S3-4 sleep in patients suffering a MACCE).

During S2 sleep, the LF/HF ratio was lower in patients with and without AHI ≥20/hour (1.9 and 2.5 vs. 4.8; P = 0.008 and P = 0.03, respectively) as well as in those with and without MACCE (1.5 and 2.4 vs. 4.8; P = 0.01 and P = 0.02, respectively) despite that there were no significant differences in the LF and HF powers themselves. Patients with and without AHI ≥20/hour had lower normalised LF (58 nu and 60 nu vs. 75 nu; P = 0.02 and P = 0.03, respectively) and higher normalised HF (37 nu and 38 nu vs. 23 nu; P = 0.04 and P = 0.02, respectively) than controls. Patients with and without MACCE also had lower normalised LF (57 nu and 60 nu vs 75 nu; P = 0.02 and P = 0.03, respectively) and higher normalised HF (38 nu and 37 nu vs. 23 nu; P = 0.04 and P = 0.02, respectively).

During REM sleep, LF was significantly lower in patients suffering a MACCE than in controls (192 ms^2 vs. 417 ms^2; P = 0.03). Patients with and without significant OSA (1.8 and 3.9 vs. 10.3; P = 0.04 and P = 0.001, respectively) had a remarkably lower LF/HF ratio as well as those *not suffering a MACCE* (2.5 vs. 10.3; P = 0.004). Patients with AHI ≥20/hour had lower normalised LF (62 nu vs. 82 nu; P = 0.002) and higher normalised HF than controls (35 nu vs. 17 nu; P = 0.003). The same was true in patients not suffering a MACCE in both normalised LF and normalised HF (66 nu vs 82 nu. and 31 nu vs. 17 nu, respectively; P = 0.009 for both). During S3-4 sleep, there were no differences in the spectral parameters between the specified patient groups and controls.

During evening wakefulness, the LF/HF ratio was significantly lower in patients with AHI ≥20/hour (2.0 vs. 5.3; P = 0.01). The patients with AHI ≥20/hour also had markedly lower normalised LF (63 nu vs. 81 nu; P = 0.005) and higher normalised

HF (33 nu vs. 18 nu; P = 0.006) than controls. The same was true in patients suffering a MACCE who also had significantly lower normalised LF (60 nu vs. 81 nu; P = 0.003) and higher normalised HF (35 nu vs. 18 nu; P = 0.006).

During morning wakefulness, the LF/HF ratio was only lower in patients with AHI ≥20/hour (2.5 vs. 5.4; P = 0.03); these patients had decreased normalised LF (64 nu vs. 80 nu; P = 0.03) and increased normalised HF (32 nu vs. 20 nu; P = 0.04). In addition, total power (996 ms^2 vs. 2174 ms^2; P = 0.03), ULF power (69 ms^2 vs. 223 ms^2; P = 0.02) and VLF power (580 ms^2 vs. 1482 ms^2; P = 0.02) were significantly lower in patients with AHI ≥20/hour; those who suffered a MACCE had decreased ULF (103 ms^2 vs. 223 ms^2; P = 0.03) and VLF (490 ms^2 vs. 1482 ms^2; P = 0.045) powers as well.

5.6.2.3 Non-linear assessments

In the DFA analyses, the fractal scaling exponent alpha 1 seemed to decrease both during sleep and wakefulness in all patients when compared to healthy controls. During evening wakefulness, the alpha 1 was significantly lower in patients with and without AHI ≥20/hour (1.11 and 1.16 vs. 1.37; P = 0.01 and P = 0.049, respectively). Those with and without MACCE also had lower alpha 1 (1.08 and 1.16 vs. 1.37; P = 0.01 and P = 0.04, respectively). In the morning, the alpha 1 was only lower in patients with AHI ≥20/hour (1.13 vs. 1.45; P = 0.002). In S2 sleep, patients with and without AHI ≥20/hour had lower alpha 1 (1.00 and 1.05 vs. 1.29; P = 0.01 and P = 0.04, respectively) as well as those with and without MACCE (1.00 and 1.04 vs. 1.29; P = 0.02 and P = 0.03, respectively). In REM sleep patients with AHI ≥20/hour had lower alpha 1 (1.06 vs. 1.43; P = 0.01) than controls as well as those *not suffering a MACCE* (1.10 vs. 1.43; P = 0.01). In S3-4 sleep, the alpha 1 did not differ significantly in any of the patient groups. Sample entropy differed only between sleep stages but was almost identical across the patient groups in a said sleep stage or during wakefulness.

5.6.3 Association of HRV with OSA and MACCE

5.6.3.1 Predictors of significant OSA and MACCE

The covariance analyses showed that none of the HRV parameters in S2 sleep as well as either during evening or morning wakefulness was able to predict incident MACCE. Furthermore, no HRV parameter was predictive of significant OSA (AHI ≥20/hour) during S2, S3-4 or REM sleep or evening wakefulness. In the morning, however, OSA with AHI ≥20/hour displayed lower fractal correlation of HRV as shown by the significantly lower alpha 1, compared to patients without such severe OSA (1.12 vs. 1.34; P = 0.02). This difference remained after adjusting for age, BMI, coronary artery disease and PAD history (P = 0.03). The unadjusted LF/HF ratio was also lower in patients with AHI ≥20/hour (2.5 vs. 3.9; P = 0.046) during morning wakefulness but the significance of this difference disappeared after the adjustments.

Patients with MACCE had lower maximum NNI (1018 ms vs. 1161 ms; P = 0.04), pNN50 (1.4 % vs. 2.7 %; p=0.04) and HF power (35 ms^2 vs. 96 ms^2; p=0.01) during REM sleep than those not suffering a major event. Of these, the difference in HF power remained significant after the adjustments (p=0.04).

Patients suffering a MACCE had lower RMSSD (13 ms vs. 25 ms; p=0.009), HF power (25 ms^2 vs. 162 ms^2; p=0.004) and normalized HF units (33 nu vs. 52 nu; P = 0.02) as well as higher LF/HF ratio (2.3 vs. 0.83; P = 0.04) and normalized LF units (65 nu vs. 46 nu; P = 0.02) during S3-4 sleep. Of these, the differences in RMSSD (P = 0.04), HF power (P = 0.03) and normalized HF units (P = 0.048) remained significant after the adjustments.

ANCOVA was also performed from S2 sleep free from apnoea and arousals (available from 57 patients, 20 with AHI ≥20/hour and 14 suffering a MACCE). In this analysis, none of the HRV parameters predicted significant OSA or MACCE.

5.6.3.2 HRV analyses with combined sleep stages

In the analyses with all sleep stages combined, lower LF power (114 ms^2 vs. 312 ms^2; P = 0.04) and lower HF power (68 ms^2 vs. 150 ms^2; P = 0.03) were associated with MACCE but these differences were not significant after the adjustments. The independent predictive value was most importantly affected by pre-existing coronary disease.

When patients with worsening OSA (10-20/hour, 20-30/hour, >30/hour) were compared to those with AHI <10/hour, higher minimum NNI (891 ms vs. 767 ms; P = 0.008), maximum NNI (1198 ms vs. 1011 ms; P = 0.02) and mean NNI (1040 ms vs. 884 ms; P = 0.006) as well as standard deviation of NNI (47 ms vs. 25 ms; P = 0.03) of the time domain parameters were associated with AHI 10-20/hour. In the frequency domain, higher VLF power (1435 ms^2 vs. 312 ms^2; P = 0.02), LF power (465 ms^2 vs. 153 ms^2; P = 0.04), HF power (249 ms^2 vs. 69 ms^2; P = 0.02) and total power (2080 ms^2 vs. 615 ms^2; P = 0.02) were predictive of AHI 10-20/hour. Patients with AHI ≥30/hour had higher NNI standard deviation (38 ms vs. 25 ms; P = 0.048) and higher RMSSD (31 ms vs. 21 ms; P = 0.02) as well as higher HF power (164 ms^2 vs. 69 ms^2; P = 0.02) than those with AHI <10/hour. While these differences were observed after the adjustments, none of the HRV parameters was predictive of AHI 20-30/hour. VLF power was higher in patients with AHI 20-30/hour and ≥30/hour but the increase in these groups was less than in those with AHI 10-20/hour and not statistically significant. Taken together, the HRV parameters did not change consistently in parallel with the AHI as OSA worsened. The HRV parameters in the analyses with combined sleep stages are detailed in table 5.

Table 5. HRV characteristics in combined sleep stages according to the severity of OSA and occurrence of MACCE.

	AHI <10 n = 18	AHI 10-20 n = 21	AHI 20-30 n = 14	AHI ≥30 n = 21	No MACCE n = 52	MACCE n = 22
HR, 1/min	68 (59-78)	58† (50*-67†)	63 (55-72)	63 (52-74)	62 (53-72)	63 (55-73)
NNI Min, ms	767 (124)	891 (126) †	830 (134)	810 (112)	828 (127)	824 (139)
NNI Max, ms	1011 (195)	1198 (163) *	1085 (174)	1157 (252)	1129 (195)	1096 (245)
NNI Mean, ms	884 (158)	1040 (141) †	958 (159)	960 (140)	970 (150)	950 (173)
NNI Dev, ms	25 [16]	47 [24] *	32 [17]	38 [36] *	39 [30]	27 [28]
NNI RMSSD, ms	21 [14]	31 [19]	21 [14]	31 [28] *	27 [22]	25 [23]
NNI pNN50, %	2.0 [6.2]	6.5 [13.6]	1.1 [6.3]	5.9 [14.1]	4.7 [14.0]	4.2 [6.6]
NNI SampEn	1.3 (0.3)	1.5 (0.2)	1.3 (0.3)	1.4 (0.3)	1.4 (0.3)	1.3 (0.3)
NNIS Total, ms²	615 [1013]	2080 [2314] *	1245 [1737]	1119 [2603]	1435 [2687]	790 [1622]
NNIS ULF, ms²	45 [138]	101 [232]	124 [210]	72 [65]	90 [185]	45 [77]
NNIS VLF, ms²	312 [541]	1435 [1200] *	722 [883]	625 [1195]	763 [1221]	408 [1201]
NNIS LF, ms²	153 [252]	465 [750] *	189 [366]	226 [785]	312 [774]	114 [275] ‡
NNIS HF, ms²	69 [71]	249 [378] *	63 [140]	164 [384] *	150 [318]	68 [142] ‡
NNIS LF/HF	2.9 [5.6]	2.5 [3.5]	3.3 [3.1]	1.4 [1.2]	2.3 [3.7]	2.1 [2.6]
NNIS nLF, nu	62 (23)	60 (19)	65 (16)	53 (19)	60 (19)	59 (23)
NNIS nHF, nu	35 (22)	38 (18)	31 (14)	42 (14)	38 (17)	36 (18)
NNI Alpha 1	1.09 (0.33)	1.07 (0.29)	1.06 (0.35)	0.93 (0.30)	1.03 (0.29)	1.03 (0.39)

Data are mean (standard deviation) or median [interquartile range] except for mean (range) for heart rate (HR). AHI = Apnea-hypopnea index, Alpha 1 = Fractal scaling exponent alpha 1, Dev = Standard deviation of NNI, HF = Power in the high frequency range (0.15-0.4 Hz), LF = Power in the low frequency range (0.04-0.15 Hz), MACCE = Major adverse cardiovascular and cerebrovascular event, ms = millisecond, nHF = normalized HF ratio, nLF = normalized LF ratio, NNI = normal-to-normal interval (i.e. time between normal beats in the electrocardiogram), NNIS = NNI spectrum, nu = normalised unit, pNN50 = Proportion of NNI >50 ms, RMSSD = Root mean square of the sum of successive differences (between adjacent normal-to-normal intervals, i.e. beat-to-beat variability), SampEn = Sample entropy, Total = Total power of the NNI spectrum, ULF = Power in the ultra-low frequency range (≤0.003 Hz), VLF = Power in the very low frequency range (0.003-0.04 Hz). One-way analysis of variance with Dunnett's post hoc was used to test for differences between each OSA severity group (AHI 10-20/hour, 20-30/hour and >30/hour) vs. AHI <10/hour. Analysis of covariance (ANCOVA) was used to test for independent differences between the OSA severity groups (same as above) and between patients with and without MACCE. The ANCOVA was adjusted for age, body mass index, presence of coronary artery disease and PAD duration (skewed variables log-transformed). *: $p<0.05$ compared to patients with AHI <10/hour; †: $p<0.01$ compared to patients with AHI <10/hour; ‡: $p<0.05$ between patients with and without MACCE (unadjusted analysis, no significant difference after adjustment). (Modified from original publication III)

6. DISCUSSION

6.1 Prevalence of OSA in patients with PAD

The prevalence of sleep apnoea is exceedingly high in patients with severe PAD requiring surgical intervention. In this study, sleep apnoea was mainly obstructive and unrelated to the common clinical signs (obesity or metabolic syndrome) or symptoms of the OSA syndrome (excessive sleepiness). Furthermore, OSA was more common in this study population than in most other previously studied patients with established risk factors or clinical manifestations of cardiovascular disease. A comparable prevalence (83 %) was reported in patients with drug-resistant hypertension (Logan et al. 2001). Since almost half of the subjects included by Logan et al. had co-morbidities predicting or indicating advanced cardiovascular disease, an overlap with the patients of this study is likely.

Obesity is generally considered to be the major single risk factor for OSA. It has also been suggested that OSA is a manifestation of metabolic syndrome and has an incremental effect on the overall atherosclerotic burden (Vgontzas et al. 2005; Drager et al. 2010). However, most patients of the present study were not obese and earlier studies have also shown that obesity is not a characteristic clinical feature of PAD (Meijer et al. 1998). Although more than half of our patients in this study also had metabolic syndrome, neither its prevalence nor the patients´ waist circumference correlated to the severity of OSA; of the diagnostic criteria of metabolic syndrome, only decreased HDL was associated with OSA. Otherwise, the multivariate analysis failed to show any relation between the severity of OSA and common risk factors of atherosclerosis, including metabolic syndrome. Of the clinical manifestations of atherosclerosis, OSA was only associated with PAD. Taken together, none of the co-morbidities or cardiovascular risk factors in this study explains the high prevalence of OSA.

The proportion of central apnoea was remarkably high but the predominant type of apnoea was still obstructive even in patients with mild left ventricular dysfunction. Following our exclusion criteria, none of the patients had clinical heart failure and only four patients had mildly decreased LVEF. Nevertheless, decreasing LVEF was still an independent predictor of OSA even in this carefully selected population despite remaining mostly in the normal range. This is in line with the earlier observations showing that OSA impairs left ventricular function (Laaban et al. 2002). Mild left ventricular dysfunction is not supposed to cause central apnoea in the magnitude observed in this study (or vice versa). Accordingly, the clinical characteristics do not explain the high prevalence of sleep apnoea in this study, and simple mechanical airway obstruction without any concomitant or alternate aetiology is unlikely.

Mounting evidence shows that sleep apnoea enhances endothelial dysfunction and arterial stiffness which are the key factors in the development of atherosclerosis (Jelic et al. 2008; Drager et al. 2007; Herrington et al. 2004) and this has also been shown in minimally symptomatic patients (Kohler et al. 2008). Importantly, these common denominators of atherosclerosis and OSA can be alleviated with CPAP treatment (Ip et al. 2004; Drager et al. 2007), potentially reversing the progression of vascular damage. The severity of OSA is independently associated with early signs of atherosclerosis and has an additive effect with hypertension on these markers (Drager et al. 2005; Drager et al. 2009). Considering that OSA is closely related to both the precursors of atherosclerosis and clinical cardiovascular disease, the high prevalence of OSA in patients with severe systemic atherosclerosis that was shown in this study is not actually surprising. Taken together, OSA appears to be an important pathophysiological factor in the development of atherosclerosis and its progression to a severe stage.

ABI values and toe pressures showed no association with the severity of OSA which speaks against a direct link between OSA and severity of PAD. This may be due to the fact that the patients included in this study already represent a severe form of PAD (requiring surgery); hence the Fontaine classification was not used. Furthermore, the anatomical extent of LEAD was not quantified. Therefore, except for the few patients presenting with critical ischaemia at baseline, there was little variation in terms of PAD severity. Studying a population with more diversity in this aspect (extent of LEAD, need and method of revascularisation, critical ischaemia), cardiovascular co-morbidities (atrial fibrillation, heart failure) or even more extensive vascular disease (e.g. renal or mesenterial atherosclerosis) could be informative. Indeed, the high prevalence of OSA has recently been replicated in patients with less severe PAD treated conservatively (Pizarro et al. 2015) and in patients undergoing PTA (Schahab et al. 2017) with an overall prevalence of 70 % and 81 %, respectively. Later studies have also shown an independent association of moderate-to-severe sleep apnoea with PAD in different ethnic groups (Shah et al. 2015; Nagayoshi et al. 2016). Thus, OSA seems to become more common in parallel with worsening PAD (and vice versa).

6.2 Possible alternate aetiologies of OSA in patients with PAD

6.2.1 Role of central apnoea

The fact that the apnoeic episodes were mixed with a remarkable central component raises the question whether central mechanisms are involved in the development of sleep-disordered breathing in PAD. Indeed, it has been shown that white matter disease of the brain is associated with the common risk factors and manifestations of atherosclerosis, including compromised lower limb circulation, and central sleep apnoea but there is no clear association with OSA (Davies et al. 2001; Longstreth et al. 2005; Robbins et al. 2005). However, white matter microstructural damage has been shown to correlate with the severity of OSA (Chen et al. 2015). Therefore,

asymptomatic ischaemic brain lesions may play a role in the disruption of central regulation of breathing during sleep in patients with severe PAD. This may account for the increased proportion of central apnoea episodes but does not explain the high prevalence of OSA *per se*. In addition, diabetes alone, via autonomic neuropathy, has been proposed to cause central apnoea by altering chemoreceptor gain and disturbing ventilatory control (Resnick et al. 2003). However, OSA is also more common in diabetic patients with autonomic neuropathy than in those without. This may be due to impaired sensory reflexes of the upper airway as well as decreased respiratory drive to the dilator muscles (Ficker et al. 1998).

6.2.2 Bidirectionality between atherosclerosis and OSA

6.2.2.1 Role of chemoreceptor feedback

The presence of OSA seems to be tightly related to the severity of atherosclerosis. This suggests that the co-existence of these two conditions may not only be due to similar risk factors but may share a common pathophysiology instead. One speculative mechanism may be that advanced vascular disease affects the compensatory mechanisms that protect from airway collapse and obstruction. It can be further speculated that systemic atherosclerosis as reflected by PAD affects the afferent circulation of arterial chemoreceptors, causing increased sensitivity to hypoxia. The resulting hyperventilation and hypocapnia could potentially decrease ventilatory drive to muscles of the upper airway. The theoretical basis for this hypothesis is laid out below.

Chronic hypoxia elicits increased sensitivity of the chemoreceptors and augmented ventilatory response in both animals and humans and may cause enlargement of the carotid body (Barnard et al. 1987; Bisgard 1994; Lahiri et al. 2000). Interestingly, nitric oxide has an inhibitory effect on carotid body function as it attenuates the chemoreceptor response to hypoxia (Prabhakar 1999). It is therefore plausible that a shortage of nitric oxide could be a potential underlying factor linking endothelial dysfunction, atherosclerosis, chemoreceptor dysfunction and respiratory dysregulation together.

Early studies have observed hyperplasia of the carotid body and corresponding changes in ventilation in patients with hypertension and myocardial hypertrophy (Edwards et al. 1971; Smith et al. 1982; Trzebski et al. 1982). Animal studies have shown severe vascular damage in the afferent vessels of the carotid body that is related to hypertension (Smith et al. 1984; Bee et al. 1989). These changes, in turn, are associated with hyperventilation and hypocapnia although the carotid body hyperplasia may be present or absent (Barer et al. 1987; Bee et al. 1989; Heath & Smith 1992). Therefore, a hypothesis has been drawn that the overactivity of the chemoreceptors may be caused by reduced blood and oxygen supply to the carotid body due to vascular damage in the afferent arterioles, resulting in carotid body hyperplasia, respiratory changes and altered gas homeostasis (Bee et al. 1989; Barer 1994). This would mean that hypertension precedes carotid body vascular damage

and causes chemoreceptor dysfunction even before the manifestation of atherosclerosis (Pfeiffer et al. 1984; Bee et al. 1989; Heath & Smith 1992). However, these findings have not been consistent in all studies with human subjects and some animal models have produced opposite results (Barer 1994), although the carotid body is enlarged in patients suffering from sustained hypoxia due to chronic lung disease (Edwards et al. 1971; Heath et al. 1982). In addition, the ventilatory response to hypoxia is physiologically blunted in continuous hypoxic conditions such as in high altitudes (Moore et al. 1986; Lahiri et al. 2000). Whether pathophysiological conditions such as severe atherosclerosis can mimic the effects of chronic hypoxia and cause chemoreceptor dysfunction is not known.

6.2.2.2 Respiratory long-term facilitation

Respiratory long-term facilitation (LTF) is a phenomenon in which intermittent hypoxia induces a progressive increase in respiratory drive that can be observed both in the motor output of the diaphragm and the upper airway dilator muscles. This stimulating effect may persist hours after the hypoxic events have subsided. LTF has been demonstrated in several animal models (Cao et al. 1992; Turner & Mitchell 1997; Mateika & Fregosi 1997). During sleep and in human subjects, LTF has been shown to manifest as increased minute ventilation and attenuated flow limitation in snorers (Babcock & Badr 1998). A later study involving patients with moderate-to-severe OSA treated with CPAP demonstrated reduced upper airway resistance in non-REM sleep during recovery from brief episodes of hypoxia but no change in minute ventilation (Aboubakr et al. 2001). It seems that LTF is mainly elicited in the enhanced action of upper airway dilators and when inspiratory flow limitation is present (Shkoukani et al. 2002; Babcock et al. 2003). Therefore, promotion of respiratory drive can be expressed both via increased ventilation efforts and preservation of upper airway patency but the latter seems to be more important. These compensation mechanisms can potentially prevent or alleviate OSA. LTF also provides a feasible explanation for the fact that 80% of patients with OSA have extensive periods of uninterrupted sleep free of apnoea (Younes 2003). LTF is age-dependent and its decline in animal models (Zabka et al. 2001; Zabka et al. 2003) is consistent with the way the prevalence of OSA behaves with age in humans (Bixler et al. 1998). Therefore, intermittent hypoxia should physiologically have a self-limiting nature in healthy subjects and factors that impair the induction of LTF can potentially exacerbate OSA (Mahamed & Mitchell 2007) but there is no direct evidence of such a close relationship between LTF and OSA in humans.

Carotid chemoreceptors are likely to play a role in the regulation of LTF. Intermittent hypoxia is required to trigger LTF, regardless of the severity of hypoxia (Mahamed & Mitchell 2007); sustained hypoxia does not work as such preconditioning (Baker & Mitchell 2000). Hypocapnia constrains LTF in rats (Olson et al. 2001) and in normal awake human subjects (Mateika et al. 2004). In humans during non-REM sleep, manifestation of LTF was observed when end-tidal CO_2 was carefully monitored and maintained in the physiological window (Aboubakr et al. 2001;

Babcock et al. 2003) or in mild hypercapnia (Harris et al. 2006). Reduction of respiratory drive by hypocapnia promotes upper airway obstruction even after mild hyperventilation and without central apnoea (Onal et al. 1986; Badr & Kawak 1996; Badr et al. 1997) in subjects already predisposed to OSA such as snorers (Warner et al. 1987; Jordan et al. 2015). Therefore, it appears that a sufficient level of CO_2 is needed to induce LTF. However, in OSA the increased response to disturbances in gas homeostasis may actually exacerbate apnoea (Charbonneau et al. 1994), suggesting that mechanisms that protect from airway obstruction are impaired.

6.2.3 Evidence from OSA patients

OSA induces adrenergic overdrive in metabolic syndrome via hypoxia-mediated chemoreceptor activation but sympathetic activation is increased also without OSA (Grassi et al. 2010). In addition, autonomic responses to chemoreceptor activation are potentiated in OSA (Narkiewicz et al. 1999) and altered chemoreflex function elicits sympathetic activation and hyperventilation (Kara et al. 2003). It can be speculated that circulatory changes in the chemoreceptors further disrupt the balance between oxygen and CO_2 which is needed to maintain airway patency. This would mean that systemic vascular disease together with autonomic dysfunction and blood gas imbalance interact in such a way that atherosclerosis worsens OSA (and vice versa).

A more recent study showed that incident new cardiovascular disease can indeed exacerbate OSA (Chami et al. 2011). Based on this study and some earlier observations, a reverse causality between sleep apnoea (both central and obstructive) and cardiovascular disease in the form of a vicious circle has been suggested (Man & Sin 2011). Proposed mechanisms include nocturnal fluid accumulation in the upper body in patients with heart failure (Yumino et al. 2010) and ventilatory instability due to low arousal threshold and an abrupt response to brief hypoventilation (Younes et al. 2001; Younes 2004; Younes 2008). The former mechanism is ruled out in this study since none of the patients had clinical heart failure. While the study by Chami et al. included patients suffering a myocardial infarction, both with or without heart failure, incident cardiovascular events promoted only *worsening* of OSA; they did not predict *de novo* OSA.

Taken together, hyperventilation and chemical imbalance may be elicited by sympathetic activation when sustained hypoxia is sensed by the peripheral chemoreceptors which is deleterious when there is desynchronised coupling of chemical drive to upper airway dilators and respiratory pump muscles. Another plausible mechanism is that the function of central chemoreceptors is impaired due to cerebrovascular disease. However, our observational study design does not allow conclusions on causal relations. In addition, much of the evidence of these speculative mechanisms is derived from animal models with insufficient data from human subjects. Furthermore, two recent studies have questioned the concept that maintaining sufficient levels of CO_2 is essential to restoring and preserving upper airway patency after apnoea (Cori et al. 2017; Cori et al. 2017). Therefore, the exact

pathophysiology of OSA in severe PAD remains obscure; it is likely that in severe atherosclerosis, several mechanisms are involved. Although OSA appears to be a characteristic feature in severe cardiovascular disease, it is unclear whether it starts to develop in the early stage of atherosclerosis along with endothelial dysfunction or in a later severe stage.

6.3 Effect of OSA on the occurrence of MACCE

The clinically most important finding in this study was that asymptomatic OSA is an independent predictor of major long-term cardiovascular and cerebrovascular events along with pre-existing coronary artery disease in patients with PAD undergoing vascular surgery. This is a novel finding in this patient group. According to our survival analysis, the impact of OSA on clinical outcome becomes significant in the first months following surgery and persists for up to five years. Age is likely to have an increasing effect on mortality after this point. While it is not surprising that coronary artery disease was common and associated with cardiovascular morbidity and mortality, the high prevalence of OSA and its association with MACCE provides an entirely new insight to the risk stratification of these patients.

The fact that the major events were also associated with decreased HDL/Chol ratio is in line with previous data indicating that impaired lipid metabolism is a principal risk factor of cardiovascular morbidity and mortality. In this study, OSA was also linked to decreased HDL/Chol ratio. Intermittent hypoxia promotes sympathetic activation, oxidative stress, systemic inflammation and endothelial dysfunction (Kohler et al. 2008; Jelic et al. 2008); a latter randomised controlled trial showed a relationship between minimally symptomatic OSA and endothelial dysfunction that was reversible with CPAP treatment suggesting a direct causality (Kohler et al. 2013). Therefore, OSA is associated with several common denominators that are also the key mechanisms in the pathophysiology of atherosclerosis. Furthermore, repeated apnoea *per se* may directly predispose to myocardial infarction through a variety of mechanisms such as reduced supply and increased demand of oxygen in the myocardium, systolic and diastolic dysfunction, and left ventricular hypertrophy (Bradley & Floras 2009). Accordingly, the current results further support the view that OSA has a close relationship with endothelial dysfunction and the pathophysiology of atherosclerosis.

Troponin release indicating postoperative AMI was rare demonstrating that the included patients had a relatively low risk of cardiovascular complications compared to standard surgical PAD patients. This may be explained by the fact that our subjects were somewhat younger and healthier (e.g. lacking the most ill patients with congestive heart failure or end-stage renal disease). The protocol was especially strict in excluding patients with atrial fibrillation and all patients with pre-existing diagnosis of symptomatic OSA syndrome, further emphasising the importance of occult OSA. The absence of several established predictors of poor prognosis suggests that significant OSA in PAD patients needing surgical revascularisation has

a strong independent predictive value for long-term mortality and in an even greater extent if clinical coronary artery disease is present as well. However, there was no relation between OSA and perioperative and immediate postoperative AMI, possibly due to very few such events. Nonetheless, the five-year mortality was similar to that observed in the previous studies.

CPAP may prevent adverse cardiovascular events in patients with severe OSA but decisive data from randomised controlled trials are lacking and obtaining such evidence (e.g. by using a sham CPAP control group) is challenging. Nonetheless, even asymptomatic patients may achieve risk reduction if CPAP is used for four hours per night or more (Peker et al. 2016; Abuzaid et al. 2017). Therefore, patients with PAD and OSA could benefit from optimal CPAP therapy. However, treatment adherence is doubtful in minimally symptomatic or asymptomatic OSA as compared to patients with EDS and the efficacy of CPAP treatment in surgical PAD patients with OSA has not been studied. Based on the current data, no recommendations for screening and treatment of OSA in this population can be given.

This study is in agreement with the concept that EDS is not relevant regarding the cardiovascular threat posed by OSA (Drager et al. 2010). On the other hand, a more aggressive pharmacologic secondary prevention even without CPAP treatment may be beneficial in this population. Furthermore, a simple and inexpensive screening method compared to complete overnight polysomnography should be established. The very close correlation of oxyhaemoglobin desaturation index with the AHI in this study supports the utilisation of overnight oximetry as the preferred means for screening. Since the threshold for significant OSA was set to AHI ≥20/hour, which means moderate or severe OSA, the risk for false positive findings with overnight oximetry is likely to be negligible. According to our current results, patients with coronary artery disease, a PAD history with a rapidly developing need for surgical treatment and impaired lipid metabolism may be a feasible group for screening and intervention in future research.

6.4 Significance of heart rate dynamics

6.4.1 Overview of the results from the HRV analyses

The aim in assessing HRV in patients with OSA and PAD was to provide a more in-depth understanding of the underlying pathophysiology. Impaired HRV is associated with autonomic dysfunction which is a common denominator of OSA and atherosclerosis as well as one of the key factors behind the adverse cardiovascular consequences of OSA. We hypothesised that if OSA turned out to be associated with impaired HRV, it could be the pivotal factor behind compromised cardiovascular adaptability in these patients. However, this was not the case since there were few HRV parameters bearing any correlation with significant OSA (AHI ≥20/hour). According to our results, measurement of HRV is not feasible for clinical risk stratification in these patients undergoing non-cardiac vascular surgery. This further

illustrates the importance of our other findings that relatively simple clinical parameters such as OSA, coronary artery disease and PAD history are superior in predicting long-term outcome in these high-risk patients.

6.4.2 HRV alterations in patients with PAD

Although decreased HRV is clearly detrimental in ischaemic heart disease, the association between HRV and PAD is more complex. Some earlier studies have shown that decreased HRV in patients with PAD has independent predictive value for cardiovascular complications and reflects autonomic neuropathy in patients with both PAD and type 2 diabetes mellitus (Mamode et al. 2001; Canani et al 2013). In this study, we observed decreasing LF power in patients with PAD compared to controls while the HF power increased to a lesser extent. One earlier study detected an *increased* LF/HF ratio in patients with PAD, whereas another study observed a trend towards a *decreased* LF/HF ratio and a favorable effect of exercise training on HRV (Goernig et al. 2008; Leicht et al. 2011). Despite demonstrating altered heart rate dynamics in patients with surgical PAD, the link of these findings with MACCE was very limited. Therefore, HRV is likely to be disturbed in the majority of these patients due to severe atherosclerosis, limiting the prognostic viability of HRV measurements. In other words, a single preoperative observation in any HRV parameter is very difficult to interpret (i.e. increased/decreased, normal/abnormal) and does not adequately serve as a means for clinical risk stratification.

6.4.3 Effect of OSA on HRV

OSA promotes sympathetic activation and corresponding alterations in spectral HRV analysis have previously been demonstrated in patients with OSA both during sleep and wakefulness (Narkiewicz et al. 1998; Dingli et al. 2003). One previous study showed the scaling exponent alpha 1 correlating closely with the AHI but this was not confirmed in another study (Penzel et al. 2003; da Silva et al. 2015). Furthermore, vagal control of heart rate during daytime is decreased in obese patients with OSA even before the onset of clinical cardiovascular disease (Balachandran et al. 2012). Interestingly, some earlier studies showed not only increased sympathetic activity in moderate OSA but also that this effect can be blunted in severe OSA with an impaired physiological increase during REM sleep (Gula et al. 2003; Kesek et al. 2009).

The minor alterations observed in heart rate dynamics in PAD patients were independently associated with MACCE in a handful of parameters and in patients with REM or S3-4 sleep available for analysis. Furthermore, these alterations did not clearly indicate breakdown of fractal heart rate dynamics related to OSA, i.e. the average scaling exponent values remained close to 1 or above (but less so during sleep). Alpha 1 was significantly lower in patients with AHI $\geq$20/hour during morning wakefulness than in those without such severe OSA, and this finding is reasonable as a consequence of potential disruption of neurocirculatory regulation

due to sleep disturbed by apnoea. Thus, DFA measurements obtained from an individual patient provide limited information with respect to determining prognosis and guiding clinical decisions in the patients of this study. Although the alterations in heart rate dynamics in patients with severe PAD may to some extent be related to OSA, the increased risk conferred by OSA in this patient group is not explained by cardiac autonomic dysfunction alone. In addition, the prognostic viability of the observed differences that were associated with MACCE is further limited by the difficulty to obtain data from REM or S3-4 sleep for analysis.

6.4.4 Interactions of PAD, OSA and HRV

The LF/HF ratio has been perceived to reflect the sympathovagal balance, at least to some extent. When the LF/HF ratio increases under physiological conditions (e.g. exercise), the scaling exponent alpha 1 increases, indicative of an enhanced fractal correlation of heart rate (Tulppo et al. 2001). This self-similarity seems to be disrupted by persistent sympathetic activation, specifically when both the sympathetic and vagal branches (i.e. accentuated sympathovagal interaction) of the autonomic nervous system are activated, resulting in compromised cardiovascular adaptability (Tulppo et al. 2005). This kind of autonomic dysfunction is known to occur in heart failure and has been shown to be associated with increased mortality (Galinier et al. 2000). One could postulate that OSA with PAD could represent a similar pathophysiological condition, i.e. continuous parasympathetic compensation is required to counter sustained sympathetic activation. Predominance of sympathetic activation as reflected by increased LF/HF ratio during both REM and non-REM sleep has been shown in patients with OSA in an earlier study (Palma et al. 2013). In the patients of this study, the combined effect of frequent apnoea (both obstructive and central), arousals and intermittent hypoxia on the LF/HF ratio seems different. Since much of the HF power is related to sinus arrhythmia caused by breathing, this spectral component may especially be affected by OSA. In other words, HRV is affected by the rhythmicity of breathing events which may compromise the general feasibility of the analysis. Indeed, the use of the LF/HF ratio as a measure of cardiac sympathovagal balance has been questioned and must be interpreted with caution in general (Billman et al. 2013). Taken together, it seems that the use of the LF/HF ratio is not feasible in patients with OSA and severe PAD. This conclusion is also supported by the diversity of the behaviour of HRV in both PAD and OSA shown in previous studies.

6.4.5 Predictive value of HRV alterations

Widespread pathologic alterations in heart rate dynamics predictive of MACCE in patients with severe PAD were not found. Since the trend towards decreasing alpha 1 during S2 sleep and wakefulness in patients suffering a MACCE was quite weak, it does not seem likely that clinically significant deterioration of fractal heart rate control would have become evident in a larger sample. However, alpha 1 was lower

in all patient subgroups than in controls, suggesting that autonomic control of HRV is altered in patients with PAD. Especially LF power was decreased consistently in all patient groups while the decreased HF power during REM and S3-4 sleep was an expectable finding and reflects impaired vagal compensation in patients suffering a MACCE. Because all of our patients had a severe form of PAD, it is feasible to suggest that their autonomic nervous system function, with or without OSA, is altered in such a way that potential differences are obscured. Conversely, it is also possible that due to our selection criteria and concomitant conservative treatment, the patients examined in this study had retained their autonomic adaptability to a certain degree. Another potential explanation to the lack of prognostic HRV alterations is that the effects of PAD, OSA and central apnoea may interact in such a way that interpretation of the HRV parameters becomes increasingly problematic.

When HRV was analysed without sleep stage selection, independent alterations predictive of MACCE were not found. Instead, some significant findings with regards to the severity of OSA were observed. Patients with AHI 10-20/hour had remarkably higher power in most of the spectral parameters especially in the VLF band. However, the findings did not correlate with the worsening of OSA since the alterations in HRV were different or not significant as the AHI progressed. For example, a further increase in VLF power should have been expected (Gong et al. 2016). In contrast with this earlier study, LF and HF power or their normalised units did not correlate consistently with the AHI. These results show that a dichotomic cut-off limit for the AHI cannot be used to assess the effect of OSA on HRV and accounting for the severity of OSA is not feasible when HRV is analysed in surgical PAD patients. It also seems that calculating nocturnal HRV generally during sleep is clinically feasible, rather than from selected sleep stages because the detrimental effects on autonomic function are not limited to the actual time of the apnoea but tend to persist over a longer period.

6.5 Study limitations

There are important limitations to be considered. Due to strict exclusion criteria the study sample is relatively small and represents a subgroup of patients with PAD with a limited degree of co-morbidity. Approximately half of the screened patients were excluded and not evaluated for OSA or its symptoms which limits the viability of conclusions concerning the lack of sleepiness related to OSA. In addition, patients with a pre-existing diagnosis of OSA were excluded in order to avoid overrepresentation of symptomatic OSA syndrome and better determine the significance of occult asymptomatic or minimally symptomatic OSA in PAD. Therefore, the amount of asymptomatic OSA is probably disproportionate and the results cannot be directly extrapolated to the general clinical population of PAD patients. On the other hand, if the oldest patients or those with heart failure or other co-morbidities were included, not only the prevalence of OSA but also the percentage of central apnoea would probably have been even higher. Caution must

therefore be taken in defining the type of apnoea (obstructive or central) or the phenotype of OSA in surgical PAD patients.

A minor limitation is that systemic atherosclerosis was determined solely by the presence of LEAD; other forms of PAD (e.g. aortic, renal or mesenterial) were not evaluated. The presence of coronary or cerebrovascular disease was determined by clinical history; routine coronary angiography or carotid ultrasound were not performed. In addition, the threshold of AHI ≥20/hour that was used to determine significant OSA is somewhat arbitrary. However, it corresponds closely to the mean and median AHI observed in this study and was also based on risk calculations with subgroups. There was no continuous trend between the increase in the AHI and the risk of MACCE but this is consistent with an earlier large cohort study showing that cardiovascular risk does not parallel the AHI in a linear fashion (Shahar et al. 2001). Therefore, we feel that the cut-off level used in this study is appropriate.

HRV could not be analysed in eleven patients, two of whom suffered a fatal MACCE during follow-up. Although the association of OSA with MACCE was also seen in the group of patients that underwent HRV analyses, the possibility still remains that existing HRV alterations associated with MACCE simply did not become evident in this particular group of patients (type II statistical error). Conversely, the statistical analysis of HRV did not control for mass significances; i.e. the sheer number of parameters and comparisons between patient groups in different sleep stages increases the likelihood of (false positive) chance findings. Furthermore, dividing the study population into four subgroups simultaneously accounting for significant OSA and MACCE (i.e. AHI<20/hour-MACCE, AHI<20/hour+MACCE, AHI≥20/hour-MACCE, AHI≥20/hour+MACCE) would have been optimal. Due to sample size and number of events, this was not possible. The small size of the subgroups in the analysis with 10/hour increments in the AHI, may have obscured potential effects of worsening OSA. In addition, non-stationarities in an HRV analysis are known to bias results toward sympathetic predominance and potentially obscure differences between groups (Magagnin et al. 2011).

There was a mismatch in age and BMI between controls and patients. The control group was intended to consist of healthy volunteers without any cardiovascular disease or significant risk factors; thus, patients with moderate-to-severe OSA were excluded. The effect of mild OSA in controls may be negligible when compared to patients with or without AHI ≥20/hour. Nonetheless, the fact that the control group was unmatched and also had patients with OSA, limits the validity of conclusions based on these comparisons.

6.6 Clinical implications and future considerations

This study strengthens remarkably the role of OSA as an important pathophysiological factor in the development and progression of atherosclerosis. OSA is highly prevalent in severe PAD and has important prognostic significance. OSA was also more common than any other risk factor or manifestation of

atherosclerosis. These patients should be recognised as a high-risk group for cardiovascular complications. However, it is not clear whether OSA is a treatable cause of increased morbidity and mortality in PAD or merely a marker of severe atherosclerosis and autonomic dysfunction. The benefit of CPAP therapy in this patient group should be investigated and treatment should more frequently be considered for the patients that are symptomatic.

OSA in this group is not caused by obesity but may share a common pathophysiology with PAD instead. Based on the absence of symptoms and the pronounced component of central apnoea, OSA associated with PAD appears to be an entirely different entity as opposed to OSA syndrome. While the theoretical basis of a bidirectional relationship between OSA and severe atherosclerosis makes sense, its scientific support is insufficient; therefore, the hypothesis of atherosclerosis as a potential cause of OSA remains speculative. The concept of any one-way or single-factor causality is probably oversimplified; instead, a multi-factorial aetiology of OSA in these patients is likely. Understanding the underlying pathophysiology is important and further studies are warranted to establish the aetiology of OSA and meet the clinical needs stated above.

7. CONCLUSIONS

The main results, according to the aims of the study, were as follows:

1. OSA is exceedingly common in patients with PAD in need of surgical revascularisation and more than half of it is moderate or severe in difficulty. OSA is neither related to obesity or metabolic syndrome in this patient group, nor characterised by EDS.
2. OSA is independently associated with postoperative major adverse events and poor long-term outcome following sub-inguinal vascular surgery due to severe PAD. The threshold for significant OSA to predict these events in this study was an AHI of ≥20/hour.
3. HRV is significantly altered in patients with PAD undergoing sub-inguinal vascular surgery when compared to healthy controls but these alterations had very limited predictive value for postoperative major adverse events. Utilisation of HRV analyses for clinical risk stratification – even in specific sleep stages – in this patient group is not feasible.
4. The influence of OSA on HRV in patients with PAD is not linearly related to the severity of OSA; HRV alterations did not explain the strong association of OSA with postoperative major adverse events.

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