Underdiagnosis of Obstructive Sleep Apnoea in Peripheral Arterial Disease

Carmen Pizarro Christian Schaefer Irene Kimeu Simon Pingel Fritz Horlbeck
Izabela Tuleta Georg Nickenig Dirk Skowasch

Department of Internal Medicine II, Cardiology, Pneumology and Angiology, University Hospital Bonn, Bonn, Germany

Key Words

Obstructive sleep apnoea · Peripheral artery disease ·
Lower extremity artery disease · Endothelial dysfunction

Abstract

Background: Obstructive sleep apnoea (OSA) has interdependently been related to the onset and progression of a large portion of atherosclerotic cardiovascular disorders. In due consideration of OSA-mediated endothelial dysfunction, its impact on peripheral artery disease is conceivable, but undefined. **Objectives:** The aim of this study was to identify the prevalence of OSA in a lower extremity artery disease (LEAD) study population. **Methods:** A total of 91 patients receiving in- and outpatient treatment for LEAD were included in this prospectively conducted trial. In addition to an angiological examination, all patients underwent nocturnal screening for sleep-disordered breathing by use of SOMNOcheck micro® (SC micro) and – depending on the results obtained – polysomnography. **Results:** Patients were principally late middle-aged (69.3 ± 10.8 years), male (71.4%) and slightly overweight (BMI 26.8 ± 3.9). Overnight screening determined a sleep apnoea prevalence of 78.0%, of which 90.1% exhibited a predominantly obstructive genesis. The mean apnoea-hypopnoea index (AHI; events/h) and oxygen desaturation index (events/h) averaged 11.8 ± 13.4 and 8.9 ± 14.2 , respectively. The individual AHI categories of non-pathological (<5), mild (5 to <15), moderate (15 to <30) and severe sleep apnoea (≥ 30) accounted for 22.0, 59.3, 13.2

and 5.5%, respectively. A distributive examination of AHI within LEAD severity groups evinced a significant association ($p = 0.047$). In cases of at least moderate sleep apnoea (AHI ≥ 15) polysomnography was performed ($n = 17$, 18.7% of the whole collective). Correlative analysis revealed a significant correlation between values obtained by SC micro recording and polysomnography, establishing the diagnostic accuracy of the screening results. **Conclusions:** OSA exhibits an important prevalence of 70.3% in LEAD patients with prior undiagnosed sleep-disordered breathing, indicating major OSA unawareness in this cardiovascular cohort. However, the impact of OSA treatment on LEAD propagation remains to be determined.

© 2015 S. Karger AG, Basel

Introduction

Lower extremity artery disease (LEAD), representing a subgroup of peripheral artery disease that in turn comprises the whole range of atherosclerotic manifestation in the non-cardiac vascular bed [1], fosters major morbidity and exhibits a worldwide prevalence of up to 12% [2]. Progressive narrowing of the arteries and the extent of the induced disequilibrium in demanded and supplied peripheral blood flow determine the clinical presentation, which could vary

C.P. and C.S. contributed equally to this work.

from a silent course or intermittent exercise-dependent claudication up to ischemic rest pain. Apart from an age-related prevalence with predominance in patients aged ≥ 70 years [3], established risk factors for the onset and progression of LEAD are consistent with those in coronary artery disease (CAD) and comprise cigarette smoking, arterial hypertension, diabetes mellitus and dyslipidemia [4, 5]. Moreover, metabolic syndrome has been identified as an additional predisposing condition [6]. On the other hand, implied obesity is the strongest risk factor for obstructive sleep apnoea (OSA) [7]. OSA is defined by a recurrent reduction or complete cessation of airflow generated by upper airway obstruction and provoking gas exchange impairment [8]. Repetitive hypoxemia actuates inflammatory processes and induces endothelial dysfunction with systemic effects [9–11]. The strong association of OSA and endothelial dysfunction elucidates the aetiopathogenic dependency of OSA and cardiovascular morbidity. Consequently, the prevalence of OSA in CAD has been shown to range from 37 to 50% [12]. In consideration of the above and in view of the confirmed correlation between LEAD and CAD, an interdependence between LEAD and OSA can be presumed. However, the rates of OSA recognition and its impact in LEAD remain indeterminate. Utriainen et al. [13] analysed the frequency of OSA in 82 patients with LEAD pre-operatively to revascularisation. They offered an apnoea-hypopnoea index (AHI) ≥ 5 episodes/h and ascertained a prevalence of 85%. Due to the study concept, only surgical patients offering advanced LEAD were examined, and its role in early LEAD stages is undefined. In the present study, we therefore aimed to prospectively investigate OSA occurrence as a function of LEAD degree of severity, with particular focus on early LEAD stages.

Methods

Study Population

A total of 91 consecutive patients aged ≥ 18 years and receiving treatment for LEAD from the University Hospital's Department of Angiology (Bonn, Germany) were enrolled in this prospective cohort trial. Dependent on their LEAD severity, participants received outpatient care or were locally hospitalised. Exclusion criteria for study enrolment comprised prior sleep-disordered breathing screening, either polygraphically or polysomnographically performed, advanced congestive heart failure including New York Heart Association (NYHA) functional classes III and IV, and intractability of drug-resistant arterial hypertension related to sleep apnoea-connected cardiovascular conditions. A standardised questionnaire-based clinical evaluation and complete appraisal of presented medical reports were utilised for the assessment of comorbidities, smoking habits and concomitant medication. All patients underwent a physical examination, angiological LEAD testing and

overnight screening for sleep-disordered breathing. In order to quantify daytime sleepiness, Epworth Sleepiness Scale (ESS) scores were assessed at the time of nocturnal sleep-disordered breathing screening. The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki. All patients gave their written informed consent to participation.

Angiological Diagnostics

Non-invasive angiological examinations were performed in conformity with the current ESC guidelines on diagnosis and treatment of peripheral artery disease [1]. The clinical staging was consistent with the Fontaine classification, with stage I defining asymptomatic course, stage IIA and IIB comprehending claudication at a walking distance exceeding or below 200 m, respectively, stage III describing ischemic rest pain and stage IV including a necrotic and/or gangrenous process. Walking distance was determined by a treadmill test and anamnestic specification. Ankle brachial index (ABI), characterising lower extremity arterial compliance, was calculated by Doppler-guided measurement of each foot's posterior tibial and dorsalis pedis arteries systolic pressure and its division by brachial systolic pressure. ABI values below a ratio of 0.9 suggested lower extremity circulatory compromise. Additional duplex ultrasound, conducted by versed angiologists, was used for completion of the ABI results and enabled assessment of the atherosclerotic plaque burden and visualization of the vascular lesion's extent and severity. Those patients offering an ABI value >1.3 , which in turn is indicative of an underlying Mönckeberg medial calcific sclerosis, were consciously included in the LEAD study cohort if duplex ultrasound corroborated LEAD presence.

Moreover, we assessed central pulse wave velocity (cPWV) and pulse wave indices (PWI) using AngE Pro8[®] (Sonoteknik Austria, Maria Rain, Austria). Serving as a marker for arterial stiffness [14], brachial-ankle cPWV exceeding 12 m/s is considered pathological. PWI is calculated by the division of brachial-determined maximal oscillatory amplitude by its ankle equivalent and subsequent multiplication by the maximal amplitude duration. PWI measurement enables detection of LEAD (by PWI-elevation >180) even in sub-clinical stages that do not offer ABI alteration [15].

Nocturnal Sleep-Disordered Breathing Screening

All participants were examined for the existence of sleep-disordered breathing by an overnight in-home portable study using SOMNOcheck micro[®] (SC micro; Weinmann Medical Technology, Hamburg, Germany). It consists of a $112 \times 30 \times 50$ -mm two-channel basic measuring unit that is attached to the patient's wrist and, apart from nasal cannula-based respiratory flow assessment [16], conducts photoplethysmographic analysis of the pulse wave amplitude (PWA), allowing for evaluation of sleep fragmentation by measurement of autonomic arousals, and differentiation between obstructive and centrally driven respiratory events [17]. We monitored the occurrence of apnoea, defined as complete cessation of airflow for at least 10 s, and hypopnoea, established by a more than 50% limitation of respiratory airflow for at least 10 s, accompanied by an oxygen saturation decrease of $\geq 3\%$. Discrimination in respect of each event's obstructive or central quality was made [17]. AHI (events/h) was categorised in line with the current American Academy of Sleep Medicine manual for scoring respiratory events in sleep [18]: non-pathological (<5), mild (5 to <15), moderate (15 to <30) and severe sleep apnoea (≥ 30). The subsequent values were additionally recorded: mean and minimal oxy-

gen saturation, oxygen desaturation index (ODI; events/h), automatic arousal index (AAI), AAI due to respiratory events, respiratory effort-related AAI (i.e. the percentage of AAI caused by increased respiratory effort), average pulse frequency and snoring proportion. Given its automatic processing of recorded data evaluation, analysis was independent of the examiner.

Polysomnography

Patients with suspected sleep apnoea exhibiting a screening AHI ≥ 15 underwent cardiorespiratory polysomnographic examination (SOMNOLab®, Weinmann Medical Technology). Performed overnight with a technologist in attendance, it comprised EEG, submental and tibialis EMG, bilateral EOG, naso-oral thermistor-based airflow measurement, ECG, fingertip oximetry, inductive plethysmographic assessment of thoracic and abdominal movements and video monitoring. Polysomnography (PSG) permitted measuring of the following physiological parameters: airflow, respiratory effort, oxygen saturation, body position, limb movement, heart rate and sleep stages. Data analysis was performed both by a computer and manually by versed technologists blinded to the clinical data.

Statistical Analysis

Descriptive statistics are presented as absolute numbers and percentages, arithmetic means ($\pm$ SD) or medians (range), when appropriate. Ordinal variables were analysed by the Kruskal-Wallis non-parametric test allowing for comparison of more than two independent samples. Post hoc analyses were conducted by Bonferroni correction. Unpaired Student's *t* test was applied for the evaluation of continuous values, and Pearson's χ^2 test for examination of categorical parameters. Spearman's rank coefficient was assessed for correlation analysis of SC micro-based and polysomnographic results. The threshold for statistical significance was set at a two-tailed *p* value <0.05 . Statistical analyses were performed using SPSS Statistics 22 software (IBM, Armonk, N.Y., USA).

Results

A total of 91 patients with angiologically proven LEAD undergoing SC micro study between July 2011 and February 2014 were analysed. The participants' demographic and clinical data are presented in table 1. At inclusion, patients were predominantly late middle-aged (69.3 ± 10.8 years), male (71.4%) and slightly overweight (BMI 26.8 ± 3.9). Continued nicotine consumption was exhibited by 42.9% of patients, offering a mean value of 13.8 ± 9.3 pack years. Diabetes mellitus, arterial hypertension, hyperlipidemia and familial disposition as established cardiovascular risk factors were present in 34.1, 86.8, 64.8 and 36.3% of cases, respectively; no intractable, drug-resistant arterial hypertension was objectified. Concomitant CAD was established in 50.6% of participants, of whom 47.7% had a history of percutaneous or surgical coronary revascularization. The percentage distribution

Table 1. Patient demographic and clinical characteristics

Patients	91
Age, years	69.3 $\pm$ 10.8
Male gender	65 (71.4)
BMI	26.8 $\pm$ 3.9
Fontaine clinical stage	
I	14 (15.4)
IIA	31 (34.1)
IIB	29 (31.8)
III	6 (6.6)
IV	11 (12.1)
Cardiovascular risk factors	
Arterial hypertension	79 (86.8)
Diabetes mellitus	31 (34.1)
Dyslipidemia	59 (64.8)
Continued nicotine consumption	39 (42.9)
Familial disposition	33 (36.3)
NYHA functional class	
I	27 (29.7)
II	19 (20.9)
Medication at SDB screening	
Aspirin	69 (75.8)
Clopidogrel	26 (28.6)
Statin	65 (71.4)
ACE inhibitor	38 (41.8)
Angiotensin II receptor blocker	20 (22.0)
β -Blocker	73 (80.2)
Calcium channel blocker	22 (24.2)
Angiological parameters	
Right dorsalis pedis artery ABI	0.92 (0.50–1.92)
Left dorsalis pedis artery ABI	0.99 (0.40–1.80)
Right posterior tibial artery ABI	1.00 (0.38–1.92)
Left posterior tibial artery ABI	1.04 (0.39–1.60)
Right PWI	211 (49–1,000)
Left PWI	172 (45–1,000)
cPWV, m/s	6.6 (2.2–19.0)

Data are presented as the total number and percentage (in parentheses), mean $\pm$ SD or median and range (in parentheses). SDB = Sleep-disordered breathing; ACE = angiotensin-converting enzyme.

of LEAD severity stages is depicted in table 1. No significant distributive differences of the above-mentioned cardiovascular risk factors, CAD or BMI were stated within the LEAD stages. All patients received at least one antiplatelet agent, and statin therapy was present in 71.4% of the study population.

In terms of dorsalis pedis artery-based measurements, the mean calculated ABI averaged 0.92 (range 0.50–1.92) for the right and accordingly 0.99 (range 0.40–1.80) for the left leg; corresponding ratios for the posterior tibial artery are delineated in table 2. Pulse volume recording demonstrated bilaterally concordant mean PWI values

Table 2. Angiological and SC micro results dependent on LEAD severity degrees

	All patients	Fontaine stage I	Fontaine stage IIA	Fontaine stage IIB	Fontaine stage III	Fontaine stage IV	p value
n	91 (100)	14 (15.4)	31 (34.1)	29 (31.8)	6 (6.6)	11 (12.1)	
Age, years	69.3±10.8	69.4±8.8	70.9±12.1	67.7±10.1	71.2±11.05	68.0±12.03	0.602
ABI							
Right dorsalis pedis artery	0.92 (0.50–1.92)	1.10 (0.78–1.50)	0.98 (0.53–1.92)	0.83 (0.50–1.49)	0.89 (0.89–1.23)	0.82 (0.68–0.94)	0.013
Left dorsalis pedis artery	0.99 (0.40–1.80)	1.17 (0.92–1.38)	0.98 (0.46–1.48)	0.96 (0.40–1.80)	1.02 (0.75–1.45)	0.72 (0.60–0.93)	0.067
Right posterior tibial artery	1.00 (0.38–1.92)	1.14 (0.87–1.48)	1.00 (0.38–1.92)	0.88 (0.49–1.48)	1.01 (0.99–1.45)	0.79 (0.69–1.25)	0.003
Left posterior tibial artery	1.04 (0.39–1.60)	1.23 (0.87–1.48)	1.03 (0.39–1.40)	1.04 (0.40–1.49)	1.01 (0.94–1.60)	0.84 (0.61–1.00)	0.048
PWI							
Right PWI	211 (49–1,000)	139 (84–278)	298 (65–1,000)	354 (90–1,000)	109 (49–129)	314 (201–623)	0.003
Left PWI	172 (45–1,000)	119 (79–173)	265 (45–761)	331 (122–1,000)	102 (51–138)	313 (204–364)	<0.001
cPWV, m/s	6.6 (2.2–19.0)	6.4 (2.2–15.2)	6.2 (2.8–15.8)	7.2 (2.3–19.0)	10.2 (6.6–12.9)	7.68±2.77	0.616
Mean recording time, h	6.86±1.61	6.62±1.93	6.85±1.54	7.15±1.44	6.95±1.34	6.38±2.10	0.822
AHI	11.78±13.44	7.34±5.31	10.50±11.38	14.51±18.75	15.95±1.48	13.83±6.79	0.047
ODI	8.92±14.16	7.01±8.22	7.00±12.83	10.69±18.16	2.10±1.77	18.24±15.34	0.153
Nocturnal oxygen saturation							
Minimal, %	81.36±6.83	80.23±8.01	82.78±5.54	80.58±7.93	84.67±2.08	78.83±5.71	0.126
Mean, %	93.99±2.19	94.46±1.51	93.93±2.37	93.83±2.61	94.50±0.71	93.67±1.37	0.732
Snoring proportion, %	12.41±16.81	16.08±20.75	17.42±18.71	6.05±9.52	2.00±1.23	2.25±2.21	0.143
Nocturnal heart rate, beats per min	63.54±9.24	60.77±10.47	63.46±9.93	64.70±7.92	64.00±3.44	66.40±8.99	0.849

Data are presented as the total number and percentage (in parentheses), mean ± SD or median and range (in parentheses).

[right leg: 211 (49–1,000), left leg: 172 (45–1,000)]. The mean cPWV was 6.6 m/s (2.2–19.0 m/s) and did not manifest significant distributive changes between the LEAD severity groups.

The sleep-disordered breathing results are summarised in table 2. The screening revealed a total prevalence of sleep apnoea of 78.0%, with a mean AHI of 11.8 ± 13.4. Mean ODI was 8.9 ± 14.2, and the mean ESS score was 6.5 ± 4.0. The percentage of patients exhibiting a score ≥10, which is indicative of excessive sleepiness, was 14.3% (n = 13).

The obstructive nature of sleep apnoea was exhibited by 64 patients (70.3%) of the total LEAD collective; 7 patients (7.7%) presented predominantly centrally driven apnoeic episodes. Among the patients with predominantly central sleep apnoea (CSA) and with regard to the established conditions for CSA susceptibility, none of the patients had suffered a previous cerebrovascular accident. Their mean age was 66.4 ± 16.2 years, with 5/7 patients being male. Yet, neither age nor gender was significantly correlated to CSA occurrence.

The percentage of patients evincing an AHI ≥15 and obtaining a subsequent cardiorespiratory polysomnographic assessment accounted for 18.7% of the entire study cohort. PSG revealed a mean total sleep time of 229.9 ± 77.2 min. With regard to sleep staging, the REM

sleep stage percentage was 9.9 ± 12.7%; stage N1, N2 and N3 sleep averaged 39.4 ± 26.9, 33.4 ± 19.7 and 17.3 ± 16.6%, respectively. This distribution indicates deprivation of REM sleep and a gain in stage N1 sleep, suggestive of sleep fragmenting disorder. PSG showed a predominantly obstructive nature of sleep apnoea in 13 patients (76.5%), whilst 3 patients (17.6%) offered predominantly centrally driven apnoea. One patient presented an AHI <5 and was considered non-pathological. The number of central apnoeic episodes in patients predominantly with PSG-based OSA accounted for 13.5 ± 13.8% of the obstructive episodes' quantity. Overnight positive airway pressure treatment was initiated in 31.3% (5/16) of patients with pathological PSG results (as defined by an AHI ≥15 irrespective of clinical symptoms, or an AHI of 5 to <15 accompanied by excessive daytime sleepiness). Distribution analysis of screening AHI values between LEAD-severity groups exhibited a significant association (p = 0.047); however, Bonferroni correction-driven single pair-wise testing of AHI classes and OSA stages within LEAD groups lacked a significant correlation (fig. 1). Correlative analysis revealed a statistical highly significant dependence of SC micro-recorded and polysomnographic-measured AHI (p < 0.001, Spearman's ρ 0.70). Likewise, interprocedural comparison of ODI affirmed the concordance of values (p < 0.01, Spearman's ρ 0.66).

Fig. 1. Sleep-disordered breathing screening-based AHI severity classes stratified by Fontaine LEAD stages.

Discussion

The present study prospectively examined the frequency of sleep apnoea in an LEAD study population. Comprehending the whole range of LEAD severity degrees, a prevalence of 78% was identified, with a vast predominance of obstructive genesis. Simultaneously, ESS-stated patient symptomatology was minor, implying that only a minority of LEAD patients might have been thought to suffer from sleep-disordered breathing. In view of an OSA occurrence of 9–24% – defined by an AHI ≥ 5 – in the unselected general population [19], our finding of a 2- to 7-fold higher OSA prevalence among LEAD patients is indicative of a mutual pathophysiological correlation.

Atherosclerotic conditions, primarily CAD, have been demonstrated to be associated with OSA in prospective and cross-sectional studies [20, 21]. Repetitive nocturnal hypoxemic stress and exhausting respiratory efforts against a collapsed upper airway induce numerous acute and chronic neural, inflammatory, vascular and metabolic mechanisms that are not restricted to a sole increase of sympathetic nerve traffic with persistence during the daytime. Systemic inflammation markers comprising C-reactive protein and serum amyloid A that have been identified to play a major role in the development of atherosclerosis are elevated in OSA, independently of BMI [22, 23]. Likewise, OSA is associated with an increase in cytokines and adhesion molecules that in turn elicit adherence of monocytes to endothelial cells and subsequently promote endothelial damage and the atherosclerotic process [9, 24]. Augmented vasoconstriction can moreover

be deduced from an OSA-triggered elevation in plasma endothelin-1 concentration as an effective vasoconstrictor [25]. Simultaneously, circulating endothelial progenitor cell levels were found to be decreased in OSA, reflecting an impaired endothelial repair capacity [26]. These multiple pro-atherosclerotic mechanisms enforce endothelial dysfunction that in turn precedes atherosclerosis [10]. Therefore, it is conceivable that a strong association with OSA does not only exist for CAD, but also for other atherosclerotic processes as a result of the above-depicted systemic effects.

With regard to the whole study population, 57.1% of patients were overweight, with obesity present in 14.3% of enrolled patients. In the subgroup of SC micro-diagnosed OSA, the percentage of overweight and obese patients accounted for 62.5 and 9.4%, respectively. Neither overweight nor obesity bore correlation to the existence of OSA ($p = 0.20$ and 0.22 , respectively). However, the distribution analysis between AHI classes indicated a trend towards a higher prevalence of overweight with increasing AHI class ($p = 0.06$), whereas obesity was not associated with the severity of OSA ($p = 0.87$). Although overweight and obesity are considered to be the strongest risk factors for OSA [27], and we have indeed observed a trend towards a higher prevalence of overweight within increasing AHI classes, no statistical significance was reached. Simultaneously, AHI was significantly linked to LEAD severity. Our multivariate analysis revealed no significant relationship between OSA occurrence and a range of established risk factors for OSA (age, gender, BMI, CAD, arterial hypertension and chronic obstructive pulmonary disease).

In a surgical study collective, Utriainen et al. [13] ascertained an OSA prevalence of 85% in 82 patients with advanced LEAD undergoing revascularisation [13]. We expanded the studied population by the inclusion of and particular focussing on patients with a less severe LEAD stage. Although the entire OSA cohort prevalence averaged 70.3%, its frequency in Fontaine clinical stages III–IV accounted for 82.4%, and was consequently in line with the observations made by Utriainen et al. [13]. Low stage LEAD was associated with a minor OSA prevalence of 50.0, 70.9 and 65.5% in Fontaine stage I, IIA and IIB, respectively.

Overnight sleep-disordered breathing examination was conducted using the SC micro screening device. It utilises photoplethysmographically assessed analysis of PWA, provoked by respiratory events and arousals [28]. It provides a measurement of PWA based upon the pulsation of the arterial blood flow-driven modulation of passing light. During obstructive respiratory events the PWA increases due to vasodilation, which is followed by a vasoconstrictive response. Haba-Rubio et al. [29] studied PWA analysis in 1,431 respiratory events and identified PWA changes to be particularly associated with obstructive sleep respiratory events, evincing relation to the magnitude of central nervous activation. The SC micro monitoring device objectified an OSA prevalence of 70.3%. Although sleep-disordered breathing screening was performed in an ambulatory setting and recordings were automatically analysed, it is worthy of note that comparison of AHI and ODI obtained by SC micro and polysomnography exhibited a statistically significant close correlation. It demonstrates the diagnostic accuracy of the recording device employed here that is in line with the findings of Sommermeyer et al. [17], who attributed an accurate distinction between obstructive and central apnoeas to the combination of nasal flow and photoplethysmographic signal assessment.

There are several limitations that should be addressed. First, the study protocol did not allot a control collective or patient randomisation that would have permitted direct comparison of OSA occurrence in LEAD and healthy participants lacking cardiovascular conditions. However, in order to make a comparison with OSA frequency in the general population, we referred to prior epidemiologic studies that have defined it to account for 9–24% [19, 30]. Second, polysomnography was solely conducted in cases in which SC micro raised suspicion of substantial sleep apnoea (AHI ≥ 15). Although Sommermeyer et al. [17] demonstrated that the automated algorithms by which the signals of photoplethysmography and nasal flow assessment are analysed and that underlie the SC micro cor-

relate significantly with manual scoring, automatic data processing confers a lower diagnostic accuracy than manual scoring and may consequently limit the study results. Nevertheless, correlation analyses evidenced the efficiency of the recordings, allowing for the assumption of the reliability of the results. Third, within the subgroup of patients undergoing PSG and presenting pathological PSG results, the vast majority of cases refused ventilation therapy initiation. We primarily ascribe this fact to the patients' minor symptomatology and lacking of illness insight, as the percentage of patients with pathological PSG that simultaneously exhibited an ESS score ≥ 10 was only 25.0%. Fourth, additional longitudinal follow-up under positive airway pressure treatment is lacking, a consideration that would contribute to identifying the impact OSA treatment exerts on the LEAD course. Finally, the included number of advanced stage LEAD patients was small, limiting an extrapolation of the observed AHI augmentation by LEAD progression. However, this is mainly attributable to our intention of primarily focussing on early stage LEAD patients as a complement of the pre-described advanced stages [13].

We conclusively identified LEAD to be accompanied by an increased prevalence of OSA in moderate and severe OSA stages, indicative of a considerable lack of awareness and recognition of OSA during LEAD treatment. Apart from the unexpected high prevalence of OSA in LEAD patients, a major finding of our study is that AHI increases with LEAD severity. It broadens the range of cardiovascular conditions to which sleep-disordered breathing is linked and implies the question of whether and to what extent sleep-disordered breathing treatment may impact on LEAD progression and prognosis, analogous with the efforts that are currently being made to clarify this interdependency in the field of chronic heart failure [31].

Acknowledgments

The authors would like to acknowledge the invaluable technical assistance of Sabine Ring and Karin Springmann. We gratefully thank Weinmann Medical Technology for providing us, free of charge, the SOMNOcheck micro[®] screening device, as well as Sonoteknik Austria for enabling us to examine cPWV and PWI by use of Ange Pro8[®].

Financial Disclosure and Conflicts of Interest

None of the authors have financial or other potential conflicts of interest to disclose.

References

- 1 Tendra M, Aboyans V, Bartelink ML, et al: ESC guidelines on the diagnosis and treatment of peripheral artery diseases: document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:2851–2906.
- 2 Novo S: Classification, epidemiology, risk factors, and natural history of peripheral arterial disease. *Diabetes Obes Metab* 2002;2:S1–S6.
- 3 Rooke TW, Hirsch AT, Misra S, et al: Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;61:1555–1570.
- 4 Smith SC Jr, Milani RV, Arnett DK, Crouse JR 3rd, McDermott MM, Ridker PM, Rosenson RS, Taubert KA, Wilson PW, American Heart Association: Atherosclerotic Vascular Disease Conference: writing group II: risk factors. *Circulation* 2004;109:2613.
- 5 Selvin E, Erlinger TP: Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. *Circulation* 2004;110:738.
- 6 Maksimovic M, Vlajinac H, Radak D, Marinkovic J, Jorga J: Relationship between peripheral arterial disease and metabolic syndrome. *Angiology* 2009;60:546.
- 7 Young T, Skatrud J, Peppard PE: Risk factors for obstructive sleep apnea in adults. *JAMA* 2004;291:2013.
- 8 Epstein LJ, Kristo D, Strollo PJ Jr, Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM, Weinstein MD; Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine: Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009;5:263.
- 9 Ohga E, Tomita T, Wada H, Yamamoto H, Nagase T, Ouchi Y: Effects of obstructive sleep apnea on circulating ICAM-1, IL-8, and MCP-1. *J Appl Physiol* 2003;94:179–184.
- 10 Ip MS, Tse HF, Lam B, Tsang KW, Lam WK: Endothelial function in obstructive sleep apnea and response to treatment. *Am J Respir Crit Care Med* 2004;169:348–353.
- 11 Ayers L, Stoewhas AC, Ferry B, Stradling J, Kohler M: Elevated levels of endothelial cell-derived microparticles following short-term withdrawal of continuous positive airway pressure in patients with obstructive sleep apnea: data from a randomized controlled trial. *Respiration* 2013;85:478–485.
- 12 Luthje L, Andreas S: Obstructive sleep apnea and coronary artery disease. *Sleep Med Rev* 2008;12:19–31.
- 13 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;41:616–620.
- 14 Katakam R, Townsend RR: What's in a pulse? *J Clin Hypertens (Greenwich)* 2006;8:140–141.
- 15 Kempczinski RF: Segmental volume plethysmography in the diagnosis of lower extremity arterial occlusive disease. *J Cardiovasc Surg (Torino)* 1982;23:125.
- 16 Morgenstern C, Randerath WJ, Schwaibold M, Bolz A, Jané R: Feasibility of noninvasive single-channel automated differentiation of obstructive and central hypopneas with nasal airflow. *Respiration* 2013;85:312–318.
- 17 Sommermeier D, Zou D, Grote L, Hedner J: Detection of sleep disordered breathing and its central/obstructive character using nasal cannula and finger pulse oximeter. *J Clin Sleep Med* 2012;8:527–533.
- 18 Berry RB, Budhiraja R, Gottlieb DJ, et al: Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events: deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2012;8:597–619.
- 19 Young T, Palta M, Dempsey J, Peppard PE, Nieto FJ, Hla KM: Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort study. *WMJ* 2009;108:246–249.
- 20 Lee CH, Khoo SM, Tai BC, Chong EY, Lau C, Than Y, Shi DX, Lee LC, Kailasam A, Low AF, Teo SG, Tan HC: Obstructive sleep apnea in patients admitted for acute myocardial infarction: prevalence, predictors, and effect on microvascular perfusion. *Chest* 2009;135:1488–1495.
- 21 Buchner S, Greimel T, Hetzenecker A, Luchner A, Hamer OW, Debl K, Poschenrieder F, Fellner C, Riegger GA, Pfeifer M, Arzt M: Natural course of sleep-disordered breathing after acute myocardial infarction. *Eur Respir J* 2012;40:1173–1179.
- 22 Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V, Somers VK: Elevated C-reactive protein in patients with obstructive sleep apnea. *Circulation* 2002;105:2462–2464.
- 23 Svatikova A, Wolk R, Shamsuzzaman AS, Kara T, Olson EJ, Somers VK: Serum amyloid A in obstructive sleep apnea. *Circulation* 2003;108:1451–1454.
- 24 Dyugovskaya L, Lavie P, Lavie L: Increased adhesion molecules expression and production of reactive oxygen species in leukocytes of sleep apnea patients. *Am J Respir Crit Care Med* 2002;165:934–939.
- 25 Allahdadi KJ, Walker BR, Kanagy NL: Augmented endothelin vasoconstriction in intermittent hypoxia-induced hypertension. *Hypertension* 2005;45:705–709.
- 26 Jelic S, Padeletti M, Kawut SM, Higgins C, Canfield SM, Onat D, Colombo PC, Basner RC, Factor P, LeJemtel TH: Inflammation, oxidative stress, and repair capacity of the vascular endothelium in obstructive sleep apnea. *Circulation* 2008;117:2270–2278.
- 27 Lee SD, Kang SH, Ju G, Han JW, Kim TH, Lee CS, Kim T, Kim KW, Yoon IY: The prevalence of and risk factors for sleep-disordered breathing in an elderly Korean population. *Respiration* 2014;87:372–378.
- 28 Grote L, Zou D, Kraiczi H, Hedner J: Finger plethysmography – a method for monitoring finger blood flow during sleep disordered breathing. *Respir Physiol Neurobiol* 2003;136:141–152.
- 29 Haba-Rubio J, Darbellay G, Herrmann FR, Frey JG, Fernandes A, Vesin JM, Thiran JP, Tschopp JM: Obstructive sleep apnea syndrome: effect of respiratory events and arousal on pulse wave amplitude measured by photoplethysmography in NREM sleep. *Sleep* 2005;28:73–81.
- 30 Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM: Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013;177:1006–1014.
- 31 Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, Levy P, Simonds A, Somers VK, Zannad F, Teschler H: Rationale and design of the SERVE-HF study: treatment of sleep-disordered breathing with predominant central sleep apnoea with adaptive servo-ventilation in patients with chronic heart failure. *Eur J Heart Fail* 2013;15:937–943.