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Unrecognised obstructive sleep apnoea is common in severe peripheral arterial disease

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ABSTRACT: Patients needing surgery for peripheral arterial disease (PAD) represent a severe form of atherosclerosis with an overall 5-yr mortality of 30% after revascularisation. The aetiology for poor post-operative clinical outcome in these high-risk patients is not fully established. Obstructive sleep apnoea (OSA) is associated with atherosclerosis and is an independent risk factor for fatal and nonfatal cardiac events. Here, we determine the prevalence of undiagnosed OSA in a homogenous group of PAD patients undergoing subinguinal surgical revascularisation.

82 consecutive patients (mean age 67±9 yrs, 52 males) with sinus rhythm and without congestive heart failure or previously diagnosed OSA were enrolled for pre-operative polysomnography and echocardiography.

OSA was present in 70 (85%) patients (95% CI 75–93%), of whom 24 (34%) had severe OSA. OSA was mostly asymptomatic, and age- and sex-adjusted multivariate regression analysis showed no relation to obesity, metabolic syndrome or any manifestation of atherosclerosis, other than PAD. Left ventricular ejection fraction ($p=0.002$) and high-density lipoprotein/total cholesterol ratio ($p=0.03$) were the only independent predictors for the severity of OSA.

Thus, prevalence of OSA is unexpectedly high in patients with PAD and is not related to classical risk factors of sleep apnoea.

KEYWORDS: Cardiovascular disease, obstructive sleep apnoea

Peripheral arterial disease (PAD) is an atherosclerotic syndrome indicating severe systemic vascular disease [1]. Patients needing surgery for PAD have a poor prognosis with an overall 5-yr mortality of 30% after revascularisation [1, 2]. The aetiology and pathophysiological mechanisms for the poor post-operative clinical outcome in PAD patients is not well established.

Severe untreated obstructive sleep apnoea (OSA) is considered as an independent risk factor for cardiovascular mortality mainly due to myocardial infarction and stroke [3–6]. The prevalence of OSA is estimated to be nearly 30% in middle-aged unselected population, but it is much higher (~50%) in populations with cardiovascular disease. >85% of patients with OSA remain undiagnosed and the majority of them are asymptomatic [3–8].

Although mounting evidence now suggest that OSA is independently associated with the development and progression of atherosclerosis, the prevalence of OSA in generalised systemic atherosclerosis has not been fully established [3, 9–12]. In order to further elucidate the link between OSA and clinical outcome in PAD patients, we decided to assess the prevalence and clinical correlates of previously unrecognised OSA in patients scheduled for lower limb surgical intervention for PAD. This study is part of a larger protocol in progress to evaluate the impact of sleep-time disorders on clinical outcome after vascular surgery in PAD patients.

METHODS

Study population

Patients aged >40 yrs with PAD referred to Turku University Hospital (Turku, Finland) for elective subinguinal revascularisation were eligible for this prospective cross-sectional study. Exclusion criteria were previously diagnosed OSA syndrome,

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congestive heart failure, atrial fibrillation or any other nonsinus rhythm, inability to co-operate, immobility, end-stage renal disease, history of coronary bypass within 3 yrs, or other major surgery within 3 months prior to enrolment. Between April 2006 and August 2010, 142 consecutive patients were considered eligible for the study and were contacted by a study nurse and inquired about their availability and interest in the study. 59 patients refused to give their consent mainly for logistic reasons and 84 patients gave their written informed consent and were enrolled. After rejection of two patients because of technically insufficient sleep studies, 82 patients were included in the final analyses. The study was approved by the Medical Ethics Committee of The Hospital District of Southwest Finland (based in Turku, Finland).

Data collection

All patients underwent a detailed clinical history and physical examination, including determination of body mass index, and measurement of waist circumference. Ankle-brachial index (ABI) and toe pressures were used to assess lower limb circulation. Echocardiography was performed before polysomnography to determine left ventricular ejection fraction (LVEF). If ABI could not be measured (critical ischaemia) or if it indicated mediasclerosis (>1.3 in diabetic patients), the values were omitted (table 1). Lipid profile was either determined preoperatively from fasting blood samples or collected from hospital records. A glucose tolerance test was performed in patients without a previous diagnosis of diabetes [13]. Coronary artery disease and hypertension were considered present if previously diagnosed with established criteria. Metabolic syndrome was diagnosed if at least three of the five following standard clinical criteria were present: elevated waist circumference (available in 76 patients) ($\geqslant$88 cm in females; $\geqslant$102 cm in males), elevated triglycerides ($\geqslant$1.7 mmol·L^{-1} or on drug treatment excluding statins), reduced high-density lipoprotein (HDL)-cholesterol (<1.03 mmol·L^{-1} in males, <1.3 mmol·L^{-1} in females, or on drug treatment excluding statins), increased blood pressure ($\geqslant$130/85 or on drug treatment) and elevated fasting glucose ($\geqslant$5.6 mmol·L^{-1} or on drug treatment), as established by the American Heart Association and the National Heart, Lung and Blood Institute [14].

All subjects underwent an overnight polysomnography (Embla/Somnologica; MedCare, Reykjavik, Iceland) in a sleep laboratory [15]. Electroencephalogram (four channels), electrooculogram (two channels) and electromyogram (one channel) were recorded for determination of the sleep stages. Respiration was monitored with a pressure transducer attached to nasal prongs for respiratory flow. A pulse oximeter with finger probe (Nonin Medical Inc., Plymouth, MN, USA) measured arterial oxyhaemoglobin saturation. A separate fingertip oximeter was utilised to record plethysmographic signal for pulse transit time calculation. The Epworth sleepiness scale (ESS) and the Berlin Questionnaire (BQ) were used to assess symptoms of sleep apnoea [16, 17].

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

	All patients	No OSA	Mild OSA	Moderate OSA	Severe OSA
Subjects n	82	12	23	23	24
Age yrs	67±9	65±7	64±10	69±8	70±8*
Male	52 (63)	7 (58)	11 (48)	14 (61)	20 (83)¶¶
Smoker	31 (38)	7 (58)	11 (48)	5 (22)	8 (33)
Metabolic syndrome	50 (61)	5 (42)	13 (57)	15 (65)	17 (71)
BMI kg·m^{-2}	27.0±4.1	26.6±3.1	26.9±4.5	26.4±4.5	27.8±3.7
Waist circumference cm					
Male	101±9	102±6	98±11	102±12	101±6
Female	102±12	104±16	105±9	97±12	98±15
Diabetes mellitus	35 (43)	6 (50)	11 (48)	11 (48)	7 (29)
Hypertension	62 (76)	8 (67)	14 (61)	20 (87)	20 (83)
CAD	30 (37)	3 (25)	7 (30)	11 (48)	9 (38)
Stroke	9 (11)	4 (33)	2 (9)	1 (4)	2 (8)
LVEF$^{\#}$ %	63 (40–80)	68 (60–77)	67 (57–79)	63 (52–77)	59 (40–80)$^{++}$
Cholesterol mmol·L^{-1}	4.3±1.0	4.3±1.2	4.3±0.9	4.5±1.0	4.3±1.1
LDL¶ mmol·L^{-1}	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	37±9	31±8	32±10¶¶
TGL§ mmol·L^{-1}	1.7±1.0	1.4±1.2	1.6±1.0	1.9±1.2	1.7±1.0
ABI ratio^{f}	0.57±0.21	0.51±0.23	0.63±0.18	0.59±0.17	0.56±0.25
Toe pressure$^{\#\#}$ mmHg	51±24	44±25	56±16	49±17	52±32
PAD history yrs	3.8±3.6	3.1±3.4	3.3±3.1	4.3±4.1	4.2±3.8
Critical ischaemia	10 (12)	4 (33)	0 (0)	2 (9)	4 (17)

Data are presented as mean±SD, mean (range) or n (%), unless otherwise stated. BMI: body mass index; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; LDL: low density lipoprotein; HDL/Chol: high-density lipoprotein/total cholesterol ratio; TGL: triglycerides; ABI: ankle-brachial index; PAD: peripheral arterial disease. $^{\#}$: n=76; ¶: n=75; $^{+}$: n=80; §: n=81; ^{f}: n=74; $^{\#\#}$: n=77. The significance of association with the severity of OSA was tested with univariate cumulative logistic regression analysis. p-values reflect the association of the variable with the severity of OSA. *: p=0.02; ¶¶: p=0.03; $^{++}$: p=0.002.

Data analysis

The polysomnographic recordings, including sleep stages and arousals, were analysed by study physicians (K.T. Utriainen and O. Polo) according to common guidelines. Apnoea was defined as an episode of complete cessation of airflow for >10 s. Hypopnoea was scored if a tidal volume reduction of >50% for a minimum duration of 10 s was associated with a 4% decline in arterial oxyhaemoglobin saturation. The apnoea/hypopnoea index (AHI) was defined as the number of the apnoea or hypopnoea episodes per hour of sleep. Arterial oxyhaemoglobin desaturation index was determined as the number of desaturations of >4% per hour of sleep, and was used instead of the AHI in four patients in whom the nasal prongs had been detached during the recording. In these patients, the oximeter signal exhibited a desaturation–resaturation pattern typical for OSA. Sleep apnoea was considered significant when the AHI was ⩾5 episodes per hour. The severity of sleep apnoea was classified as mild (AHI 5–15), moderate (AHI 15–30) or severe (AHI >30) [15]. Central and obstructive episodes of apnoea were distinguished according to the respiratory swing observed in pulse transit time, as previously validated [18, 19]. Pulse transit time was calculated from the electrocardiogram and fingertip plethysmography signals using appropriate software (WinCPRS; Absolute Aliens, Turku, Finland).

Statistical analysis

The prevalence of OSA and each of its severity degree was determined and confidence intervals were calculated using binomial distribution. Significance of association of the severity of OSA (*i.e.* response variable) with each clinical variable shown in table 2 was first analysed using cumulative logistic regression models. The independent predictive value for the severity of OSA of each clinical variable was determined using a stepwise (variables with p>0.1 significance of association excluded) age- and sex-adjusted multivariate analysis. Due to the small number of patients with no OSA, the significance of the predictors for the occurrence of OSA in general was not tested separately. Instead, the severity of OSA was used as an ordinal dependent variable that also included patients with no OSA. The cumulative odds ratio was calculated corresponding to a change equal to standard deviation of the predictor. The statistical analyses were performed with SAS 9.2 software for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

Demographic features and clinical data of the patients are summarised in table 1. Sleep variables are described in table 2 and details of long-term medication in table S3. As expected, most of the patients had other manifestations of cardiovascular disease or their risk factors. Although most of the patients were nonobese, metabolic syndrome was common but was not related to of the severity of OSA. All of the included subjects were outpatients and most of them were independent in everyday activities. Eligible patients refusing their consent were significantly older (aged 71 yrs *versus* 67 yrs; p=0.02), but did not differ in any of the available clinical parameters (data not shown).

Sleep apnoea (AHI ⩾5 events per hour of sleep) was observed in 70 (85%; 95% CI 76–92%) out of 82 patients. OSA was mild in 23 (28%), moderate in 23 (28%) and severe in 24 (29%) subjects. Oxyhaemoglobin desaturation index (mean 23 h^{-1}, interquartile range 8–35) and the AHI (mean 24 h^{-1}, interquartile range 8–36) had a high correlation in the whole study population (Spearman's coefficient r=0.93). The episodes of apnoea were predominantly obstructive (proportion of central apnoea 0–40% and mean 23%, in all patients from all respiratory events). The proportion of central apnoea was similar in all categories of OSA. LVEF was mildly decreased (40–49%) in four patients with severe OSA; the rest of the patients had normal LVEF (>50%).

The ESS and BQ scores were low in the majority of the patients and failed to correlate with the severity of OSA (table 2). The ESS was pathological (⩾11) in five patients with mild OSA, two with moderate OSA and one with no OSA.

The LVEF and HDL/total cholesterol ratio (HDL/Chol), lowest arterial oxygen saturation (S_{a,O_2} Nadir), male sex and age were the only variables associated with the severity of OSA (table 1), but no relation to obesity, metabolic syndrome or any manifestation of atherosclerosis, other than PAD, was observed. In this patient group limited to severe PAD there

TABLE 2 Sleep variables according to severity of obstructive sleep apnoea (OSA)

	All patients	No OSA	Mild OSA	Moderate OSA	Severe OSA
Subjects n	82	12	23	23	24
BQ 2–3[#]	36 (44)	4 (33)	9 (39)	12 (52)	11 (46)
ESS score[#]	5.2 (0–17)	4.8 (1–12)	5.9 (0–17)	5.7 (0–11)	4.2 (0–10)
EDS (ESS >10)	8 (10)	1 (8)	5 (22)	2 (9)	0 (0)
Arousal index events·h^{-1}	21±10	13±7	17±9	22±10	27±9[¶]
S_{a,O_2} nadir %	83±7	88±3	85±5	83±6	79±8[+]
S_{a,O_2} mean %	93±3	93±2	93±2	93±3	92±3
S_{a,O_2} T90 min	29±59	14±32	20±46	15±32	57±85[§]

Data are presented as n (%), mean (range) or mean±SD, unless otherwise stated. BQ 2–3: Berlin Questionnaire (⩾2 positive categories indicate a high risk of OSA); ESS: Epworth sleepiness scale; EDS: excessive daytime sleepiness; S_{a,O_2}: arterial oxygen saturation; S_{a,O_2} T90: cumulative time for <90% S_{a,O_2}. The significance of association with the severity of OSA was tested with univariate cumulative logistic regression analysis. p-values reflect the association of the variable with the severity of OSA. [#]: n=79; [+]: p=0.0001; [¶]: p<0.0001; [§]: p=0.02.

was no correlation between the AHI and the severity of PAD, as measured by ABI and toe pressures. In the age- and sex-adjusted multivariate analysis (arousal index, S_{a,O_2} nadir and time below 90% saturation excluded), LVEF (cumulative OR 0.44, 95% CI 0.26–0.72; p=0.002, corresponding to a change equal to SD 8%-point) and HDL/Chol (cumulative OR 0.58, 95% CI 0.37–0.90; p=0.03, corresponding to SD 10%-point) remained significant independent predictors for the severity of OSA. Decreasing percentages in both parameters marked the worsening of OSA.

DISCUSSION

The main finding of this study was that the prevalence of sleep apnoea is unexpectedly high in patients with PAD requiring surgical intervention. Diagnosed sleep apnoea was mainly obstructive and unrelated to the clinical signs (either obesity or metabolic syndrome), or to the symptoms of the conventional OSA syndrome (excessive sleepiness).

Sleep apnoea in cardiovascular disease is conventionally linked with congestive heart failure. Following our exclusion criteria, none of the patients had clinical heart failure and only four patients had mild left ventricular systolic dysfunction. Nevertheless, decreasing LVEF remained as an independent predictor of the AHI even in this carefully selected population. This finding may support the earlier observations showing that OSA impairs left ventricular function [20]. It is also notable that decreasing LVEF was associated with the worsening of OSA despite remaining mostly in the normal range.

Obesity is considered the single major risk factor for OSA. It has been suggested that OSA is a manifestation of the metabolic syndrome and potentiates its effect on the overall atherosclerotic burden [21, 22]. However, most patients in our study were not obese. This is in line with earlier observations on clinical characteristics of PAD [23]. Although more than half of our patients had metabolic syndrome, neither its prevalence nor the patients' waist circumference correlated with the severity of OSA suggesting that OSA is not a manifestation of metabolic syndrome in this patient population. In addition, current multivariate analysis did not show any relationship between the severity of OSA and any manifestation of atherosclerosis (*e.g.* hypertension, coronary artery disease or stroke) other than PAD. Accordingly, none of the co-morbidities or cardiovascular risk factors in this study explains the high prevalence of OSA. Consequently, the aetiology of OSA in this patient group remains undetermined.

Mounting evidence show that sleep apnoea enhances endothelial dysfunction and arterial stiffness, the key factors in the development of atherosclerosis [10–12, 24–26]. The prevalence of sleep apnoea in our PAD patients is higher than in any other previously reported population with manifestations of atherosclerosis, with earlier studies showing 30–58% prevalence of OSA in coronary artery disease and 30–80% prevalence in arterial hypertension [3, 4, 8]. Current results support these earlier studies, showing a close relationship between atherosclerosis and OSA. However, reasons for the observed high prevalence can only be speculated as our study design does not allow any conclusions on causal relationships. According to a recent study, serious incident cardiovascular disease can exacerbate sleep apnoea implying a reversed causal pathway [27]. An alternate aetiology to simple mechanical airway obstruction is also supported by this study, revealing a higher proportion of central apnoea than has been found in earlier studies [28]. It has been shown that cerebral white matter lesions are associated with the common risk factors and manifestations of atherosclerosis, including compromised lower limb circulation [29]. Furthermore, white matter disease is known to be related to central sleep apnoea [30]. Therefore, the presence of asymptomatic ischaemic brain lesions may account for the increased proportion of central apnoea episodes, but this does not explain the high prevalence of sleep-disordered breathing *per se*. Further studies are warranted to establish the aetiology of OSA in patients with severe atherosclerosis.

There are important limitations to be considered. The study design was cross-sectional without any possibility to establish causality. Furthermore, it is difficult to assess the association of OSA and PAD independent of age and the co-morbidities that are commonly associated with both conditions. Due to strict exclusion criteria, our study sample is small and represents a subgroup of patients with PAD with a limited degree of comorbidity. Therefore, our results cannot be directly extrapolated to the general clinical population of PAD patients. The modest size of the study also limits the weight of statistical conclusions. Our strict exclusion policy aimed at a homogenous population without confounding factors, excluding the oldest patients and the most severe cases of PAD, as well as all patients with clinical heart failure who are likely to have a significant prevalence of central sleep apnoea [3]. Taken together, the potential biases arising from patient selection should underestimate instead of overestimating the real clinical prevalence of sleep apnoea in PAD patients. However, systemic atherosclerosis was determined solely by the presence of PAD; the status of other vascular beds (*e.g.* coronary, carotid and renal) was not specifically evaluated. The exact nature of apnoea in this population must also be interpreted with caution due to the considerable proportion of central episodes.

We conclude that asymptomatic OSA is exceedingly common and often under-recognised in severe PAD. Studies in larger populations and outcome data are warranted to clarify the significance of this finding.

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CLINICAL TRIAL

This study is registered at www.ClinicalTrials.gov with identifier number NCT00712946.

STATEMENT OF INTEREST

A statement of interest for T.M. Salo and the study itself can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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