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An independent association between obstructive sleep apnoea and coronary artery disease

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An independent association between obstructive sleep apnoea and coronary artery disease. Y. Peker, H. Kraiczi, J. Hedner, S. Löth, Å. Johansson, M. Bende. ©ERS Journals Ltd 1999.

ABSTRACT: Previous studies of sleep and breathing suggest an independent association between coronary artery disease (CAD) and obstructive sleep apnoea (OSA) in middle-aged males and females. These studies, however, were criticized because they did not properly adjust for all important confounding factors. In order to better control for the impact of these confounders, a case-control study was performed, matching for age, sex and body mass index (BMI), and additionally adjusting for hypertension, hypercholesterolemia, diabetes mellitus and current smoking.

A consecutive selection of 62 patients (44 males and 18 females, mean age 69 yrs, range 44–88 yrs) requiring intensive care for angina pectoris or myocardial infarction at the County Hospital of Skaraborg, Skövde, Sweden, as well as 62 age-, sex- and BMI- matched control subjects without history or signs of heart disease underwent an overnight sleep/ventilatory monitoring study. The time interval between discharge from the intensive care unit and the overnight study ranged between 4 and 21 months.

OSA, defined as a Respiratory Disturbance Index (RDI) of $\geq 10 \cdot h^{-1}$, was present in 19 CAD patients but only in eight control subjects (p=0.017). Using a univariate logistic regression analysis, current smoking (odds ratio (OR) 8.1, 95% confidence interval (CI) 2.2–29.0), diabetes mellitus (OR 4.2, 95% CI 1.1–16.1) and OSA (OR 3.0, 95% CI 1.2–7.5), but not hypertension (OR 1.5, 95% CI 0.7–3.2) and hypercholesterolaemia (OR 1.8, 95% CI 0.7–4.1) were significantly correlated with CAD. In a multiple logistic regression model, current smoking (OR 9.8, 95% CI 2.6–36.5), diabetes mellitus (OR 4.2, 95% CI 1.1–17.1) and OSA (OR 3.1, 95% CI 1.2–8.3) all remained independently associated with CAD.

In summary, these data suggest a high occurrence of obstructive sleep apnoea in middle-aged and elderly patients with coronary artery disease requiring intensive care, which should be taken into account when considering risk factors for coronary artery disease.

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Coronary artery disease (CAD) is associated with a high mortality. Male sex, obesity, smoking, diabetes mellitus, hypertension and hypercholesterolemia are all traditionally considered as risk factors for CAD. Obstructive sleep apnoea (OSA) is common in the adult population [1]. A substantial proportion of patients with OSA are overweight [2] and suffer from systemic hypertension [3]. Retrospective studies suggest that untreated OSA is associated with increased mortality [4], which may be due to coexisting cardiovascular morbidity [5]. Previous studies of sleep and breathing in CAD patients suggest an independent association between CAD and OSA in middle-aged males [6, 7] and females [8]. These studies [6, 7], however, were criticized because they did not properly adjust for all of the important confounding factors [9]. Moreover, it is unclear whether the association between OSA and CAD remains independent when including elderly subjects in the analysis.

In order to better control for the impact of these confounders, a case-control study was performed matching for age, sex and body mass index (BMI) in addition to adjusting for hypertension, hypercholesterolemia, diabetes mellitus and smoking.

Subjects and methods

Patients

During a period of 6 weeks in August–September 1993, all patients requiring intensive care for angina pectoris and/or myocardial infarction (MI) at the Dept of Cardiology at the County Hospital of Skaraborg, Skövde, Sweden were consecutively included as cases with CAD. The angina pectoris diagnosis was based on standard criteria, *i.e.* prolonged chest pain with typical changes of the electrocardiogram (ECG) and a therapeutic response to nitroglycerine administration. Exercise testing and coronary angiography were performed in patients requiring further diagnostic investigation, and in patients where angioplasty or surgical intervention could be considered. The diagnosis of MI (current or former) was based on standard criteria, *i.e.* prolonged chest pain, typically evolving ECG and two creatine phosphokinase-isoenzyme-B (CPK-B) values >0.2 mM within 10–20 h after the onset of the chest pain. Out of all eligible cases (n=97), 12 were lost due to early death, and four due to the development of

Table 1. – Anthropometric and clinical characteristics as well as sleep questionnaire results of patients with coronary artery disease and control subjects

Variable	Patients	Controls	p-value+
Subjects	62	62	
Age yrs	69.0±10.6	68.7±9.9	Matched
Sex male/female	44/18	44/18	Matched
Body mass index kg·m^{-2}	28.4±4.7	28.3±4.6	Matched
History of snoring	40	32	0.145
History of witnessed apnoeas	13	12	0.823
History of sleep fragmentation	22	9	0.007
History of nocturia	20	10	0.036
History of night sweating	15	13	0.669
History of excessive daytime tiredness	31	7	<0.001
Obstructive sleep apnoea	19	8	0.017
Hypertension	26	20	0.265
Serum total cholesterol >5.0 mM	51	45	0.198
Serum total cholesterol ≥6.5 mM	22	18	0.442
Serum total cholesterol ≥8.0 mM	7	2	0.084
Current smoking	18	3	<0.001
Smoking history (current or former)	39	31	0.148
Diabetes mellitus	11	3	0.023

Data are presented as n or mean±SD. +: Chi-squared test.

severe cardiac failure or stroke during the intensive care period. The remaining 81 patients were asked to complete a simple questionnaire concerning symptoms associated with OSA (see below) and were referred to the sleep laboratory. After discharge from the hospital, 10 patients had unstable and fatal lapse due to severe cardiac failure and nine patients refused participation in the sleep study. Consequently, 62 patients (44 males and 18 females, mean age 69 yrs, range 44–88 yrs) underwent overnight sleep/ventilatory monitoring in a stable clinical condition (New York Heart Association (NYHA) Classification, functional class I or II) [10]. The time interval between hospitalization in the intensive care unit and the overnight study ranged from 4 to 21 months. At the time of discharge from the hospital, the patients had no signs of left ventricular heart failure on chest radiograph and none of them had MI, stroke or hospital admission due to cardiac failure within 4 months of the sleep study. Current or previous MI was documented in 48 (77%) patients at the study entry. Angina pectoris without previous MI was found in 14 patients and the diagnosis was confirmed by exercise testing and/or coronary angiography in 11 of these cases. In the remaining three patients (age >80 yrs), diagnosis was based on a history of prolonged chest pain, typical ECG changes and a therapeutic response to nitroglycerine administration, only. Data concerning other traditional risk factors (see below) were obtained from all participating patients during the period in the intensive care unit (table 1). The patients with CAD were subsequently analysed in subgroups, depending on a diagnosis of OSA, concerning clinical characteristics and ongoing pharmacological treatment at the time of the overnight sleep study (table 2).

Table 2. – Anthropometric and clinical characteristics as well as medications of subgroups of patients with coronary artery disease (CAD) at the time of the overnight sleep study

Variable	CAD with OSA	CAD without OSA	p-value+
Anthropometric or clinical characteristic			
Subjects	19	43	
Male sex	15 (78.9)	29 (67.4)	0.356
Age yrs	71.5±12.1	67.8±9.7	0.214
Body mass index kg·m^{-2}	29.7±4.9	27.9±4.5	0.150
Respiratory Disturbance Index events·h^{-1}	17.5±8.3	4.9±2.3	<0.001
History of myocardial infarction	14 (73.7)	34 (79.1)	0.640
Concomitant central sleep apnoea	2 (10.5)	5 (11.6)	0.900
Hypertension	10 (52.6)	16 (37.2)	0.257
Hypercholesterolaemia	16 (84.2)	35 (81.4)	0.789
Diabetes mellitus	5 (26.3)	6 (14.0)	0.240
Current smoking	3 (15.8)	15 (34.9)	0.127
Smoking history (current or former)	13 (68.4)	26 (60.5)	0.550
Medication			
β-blockers	12 (63.2)	33 (76.7)	0.269
Nitrates	14 (73.7)	22 (51.2)	0.098
Calcium antagonists	10 (52.6)	12 (27.9)	0.061
Diuretics	11 (57.9)	13 (30.2)	0.039
Angiotensin-converting enzyme inhibitors	6 (31.6)	8 (18.6)	0.260
Digoxin	2 (10.5)	3 (7.0)	0.640

Data are presented as n(%) or mean±SD and were analysed using Student's t-test. +: Chi-squared test for categorical variables. OSA: obstructive sleep apnoea.

Control subjects

A control group of volunteers without known heart problems was recruited by a local newspaper advertisement. The advertisement was formulated as "we aim to investigate volunteers, 44–88 yrs old, without any heart problems, in order to compare risk factors for heart disease". The investigations to be performed were not disclosed in the advertisement in order to avoid a control group with a bias towards subjects with sleep related problems. Age, sex, body weight and height data for all volunteers (n=571) were collected in a database (Microsoft Access; Microsoft Corporation, Redmond, WA, USA), and BMI calculated for each subject. A computer-based matching procedure was undertaken in order to identify 62 controls. A control subject of the same sex, age and BMI was individually matched to each patient. None of the selected controls reported any symptoms of CAD upon active questioning, and a standard ECG was obtained. One subject with ECG signs of a previous quiet MI and one subject who refused to participate in the overnight sleep study were replaced from the computer-generated matching list. Blood pressure (BP) was measured sphygmomanometrically after a minimum of 15 min supine rest using an appropriately sized arm-cuff. In subjects with a recorded systolic BP ≥160 mmHg and/or diastolic BP ≥95 mmHg, at least two additional recordings of BP were obtained on separate days. All medications and smoking habits were documented. Blood samples were drawn after a

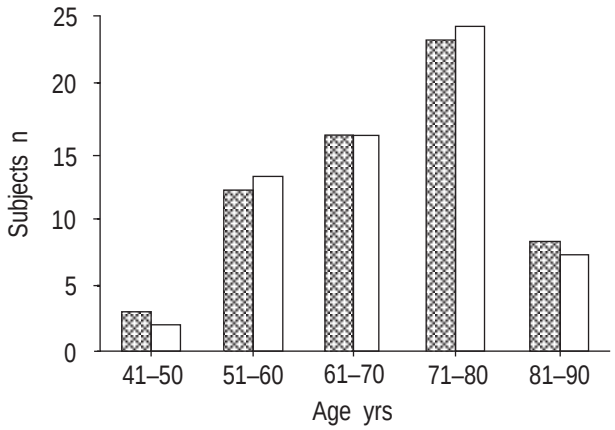

Fig. 1. – Age distribution in patients with coronary artery disease (▩) and control subjects (□) at the time of the overnight sleep study.

minimum fasting period of 8 h, and concentrations of total serum cholesterol and blood glucose were determined. The sleep questionnaire was completed in the same way as in the patients with CAD. The overnight sleep/ventilatory monitoring study was performed within 3 months of recruitment of the volunteers according to a procedure identical to that used for the patients with CAD (see below).

All subjects gave informed consent to participate in the study. The study protocol was approved by the ethics committee of the University of Gothenburg.

Basal diagnostic procedure for obstructive sleep apnoea

The self-administered sleep questionnaire included questions with yes/no alternatives concerning history of snoring, witnessed apnoeas, sleep fragmentation, nocturia and night sweating as well as excessive daytime tiredness before the current hospitalization. All subjects (n=124) underwent a standard investigation for the diagnosis of OSA in the sleep laboratory of the Dept of Otorhinolaryngology, County Hospital of Skaraborg, Skövde, Sweden. Alcohol consumption or intake of sedative medication was not allowed within 2 days of the investigation. The sleep study, lasting at least 6 h after sleep onset, included nocturnal recording of respiratory and body movements and ballistocardiogram (BCG) *via* a static charge-sensitive bed (SCSB) (Bio-matt; Biorec OY, Turku, Finland), as well as the monitoring of arterial oxygen saturation (S_{a,O_2}) *via* a finger probe (BIOX 3740; Ohmeda, Boulder, CO, USA). All signals were continuously sampled, displayed on-line and stored in a computer (BR11 software; Biorec Oy, Helsinki, Finland). An increase in the amplitude of respiratory movements with a simultaneous increase in respiratory variation in BCG and a subsequent body movement (arousal movement) was recorded as an obstructive event according to the definition of ALIHANKA [11]. Central apnoeas were recorded when the amplitude of respiratory movements decreased with a simultaneous decrease in the variation of the BCG [12]. A decrease in oxygen saturation ≥4% was defined as a significant desaturation. The diagnosis of OSA was based on a Respiratory Disturbance Index (RDI), defined as the average number of obstructive events with significant desaturations per hour of supervized estimated sleep, of ≥10 events·h^{-1}. The RDI was scored manually by the same physician (S. Löth).

Definition of traditional risk factors

Hypertension was defined as ongoing pharmacological antihypertensive treatment and/or blood pressure 160/95 mmHg, measured on at least three different days [13]. Hypercholesterolemia was defined as a total serum cholesterol concentration >5.0 mM [14]. Diabetes mellitus was diagnosed when subjects were receiving insulin or oral antidiabetic drugs, or had a fasting blood glucose concentration >6.7 mM on three separate occasions. Subjects were classed as current smokers, former smokers (those who had stopped smoking at least 6 months before inclusion in the study), and those who had never smoked.

Statistics

Continuous variables are given as mean±SD. Subjects were compared using a paired t-test, and the subgroups of CAD patients using Student′s t-test for variables measured on a continuous scale, and the Chi-squared test for categorical variables. Differences with p-values <0.05 were considered significant. Using a univariate logistic regression (STATISTICA^{TM}; StatSoft Inc., Tulsa, OK, USA), odds ratios (ORs) for the relationship between OSA as well as traditional risk factors for CAD were calculated. All significant variables that correlated with CAD in the univariate analyses were subsequently included in a multiple logistic regression model, and corrected ORs were calculated from the regression coefficients. All ORs are presented with their 95% confidence intervals (CI).

Results

Figures 1 and 2 illustrate the age and BMI distribution of all subjects. Patients and control subjects were carefully matched for age, sex and BMI. Subjective symptoms regarding history of snoring, witnessed apnoeas and night sweating did not differ significantly between the groups while sleep fragmentation, nocturia and excessive daytime tiredness were more common in CAD patients (table 1). Overnight sleep studies revealed OSA in 19 CAD patients but only in eight control subjects (p=0.017). The sleep apnoeics in the CAD group had a higher RDI than the sleep apnoeics in the control group (fig. 3). Moreover, out of the eight control subjects with OSA, seven were asymptomatic. As shown in table 2, CAD patients with OSA were slightly older and more obese than those without OSA, and there was a relative overrepresentation of male sex in the OSA subgroup, although the differences were not statistically significant. The proportion of cases with a history of MI was similar in both subgroups at the time of the sleep study. All patients were in a stable condition (NYHA class I or II), and none of them had MI, stroke or hospital admission due to a cardiac failure within 4 months of the sleep study. No patient demonstrated purely central apnoeas. Concomitant central apnoea was observed in seven patients, all presenting with a predominance of obstructive events (table 2). Only two of these patients were classed as sleep apnoeics (RDI ≥10 events·h^{-1}).

Hypertension and diabetes mellitus were more common in CAD patients with OSA compared to those without OSA, but the differences were not statistically significant.

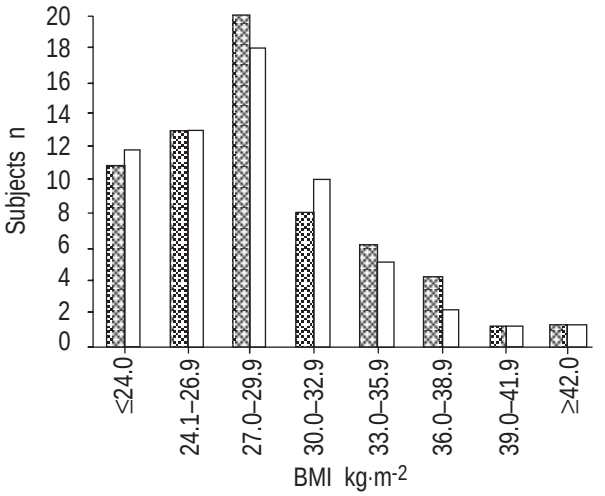

Fig. 2. – Body mass index (BMI) distribution in patients with coronary artery disease (▩) and control subjects (□) at the time of the overnight sleep study.

Hypercholesterolemia and positive smoking history did not differ between the subgroup of CAD patients, while current smoking was more common in the non-OSA group. At the time of the sleep study, ongoing pharmacological treatment with nitrates, calcium antagonists, angiotensin converting enzyme-inhibitors and diuretics were more common in CAD patients with OSA compared to the patients without OSA (table 2).

As shown in table 1, hypertension was diagnosed in 26 patients compared to 20 control subjects, of which 11 did not receive any antihypertensive treatment. The prevalence of hypercholesterolemia did not differ significantly between the groups, even when using different cut-off levels adapting a definition of moderate (≥6.5 mM) or marked hypercholesterolemia (≥8.0 mM) [14]. One patient, but no control subjects received cholesterol lowering medication. Diabetes mellitus was approximately four times more prevalent in CAD patients compared to controls. Positive smoking history did not differ significantly between the groups but current smoking was approximately six-fold more common in patients compared to controls (table 1).

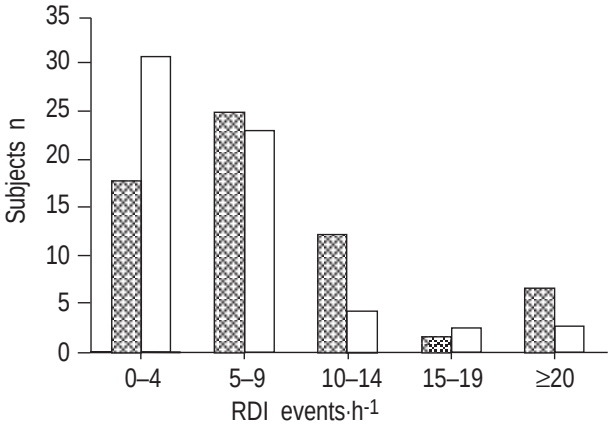

Fig. 3. – Respiratory disturbance index (RDI) distribution in patients with coronary artery disease (▩) and control subjects (□).

Table 3. – Explanatory variables associated with coronary artery disease (univariate logistic regression analysis)

Variable	Odds ratio	95% CI	p-value
Current smoking	8.1	2.2–29.0	0.002
Diabetes mellitus	4.2	1.1–16.1	0.035
Obstructive sleep apnoea	3.0	1.2–7.5	0.021
Hypertension	1.8	0.7–4.1	0.268
Hypercholesterolaemia	1.5	0.7–3.2	0.203

CI: confidence interval.

In a univariate logistic regression analysis, current smoking, diabetes mellitus and OSA, but not hypercholesterolemia and hypertension, were significantly correlated with CAD (table 3). In a multiple logistic regression model, current smoking, diabetes mellitus and OSA all remained independently associated with CAD (table 4).

Discussion

This study has demonstrated an increased prevalence of OSA in middle-aged and elderly patients with CAD compared to age-, sex- and BMI-matched controls without CAD. OSA was independently associated with CAD after adjustment for traditionally considered risk factors.

A number of recent studies have suggested an association between sleep disordered breathing and vascular disease, including CAD, hypertension and cerebrovascular disease [6–8, 15–20]. A high occurrence of nocturnal myocardial ischaemia in association with obstructive apnoeas and sustained oxygen desaturation was reported by KOEHLER *et al*. [17] in 30 patients with and without CAD, as well as in an uncontrolled cross-sectional study by DE OLAZABEL *et al*. [18]. A depression of the segment between the S and T waves of an ECG, (a typical ECG indication of myocardial ischaemia), has been reported to be relatively common during sleep in OSA patients without a history of CAD, and OSA treatment with nasal continuous positive airway pressure (nCPAP) reduced these ST-depressions [19]. Moreover, sleep apnoea was found in nine out of 10 patients with severely disabling angina pectoris and nocturnal angina [20], and the number of nocturnal myocardial ischaemic events was reduced after treatment of the breathing disorder. In a wider epidemiological perspective, sleep apnoea has also been associated with MI [6]. Among 101 middle-aged survivors of acute MI, an apnoea index (AI) exceeded 5 in 36% compared to 4% of 63 age-matched controls. AI remained as an independent predictor even after statistical adjustment for age, BMI, hypertension, smoking and cholesterol level. Two additional case-control studies of 142 males and 102 females, respectively, <70 yrs old, with symptomatic and angiographically verified CAD have been performed [7,

Table 4. – Explanatory variables associated with coronary artery disease (multiple regression analysis)

Variable	Odds ratio	95% CI	p-value
Current smoking	9.8	2.6–36.5	0.001
Diabetes mellitus	4.2	1.1–17.1	0.045
Obstructive sleep apnoea	3.1	1.2–8.3	0.025

CI: confidence interval.

8]. An apnoea-hypopnoea index >10 events·h^{-1} was almost twice as common in male and 3-times more prevalent in female CAD patients when compared to their age-matched controls. It is unclear whether the association between OSA and CAD remains independent when including elderly people in the analysis. Moreover, in a recently debated paper by WRIGHT *et al*. [9], most studies on the association between OSA and cardiovascular diseases were criticized, mainly because they did not properly adjust for all of the important confounding factors.

The present study, exploring the possibility of a causal link between OSA and CAD, may be criticized for its case-control design. To the authors' knowledge, this study is the first study of its type to include elderly people, and matching not only for age and sex but also for BMI. Although considerable effort was made to provide good matching, a true population based prospective design may have been preferable. However, no prospective study should be started without a preceding case-control study in order to check that a suspected association actually manifests itself. In clinical practice, when considering the serious haemodynamic changes which have been associated with OSA [15], it appears unethical to set up a "prospective, double-blind and placebo-controlled study design", as suggested by WRIGHT *et al*. [9]. Not only would randomization of OSA patients to placebo treatment mean a potentially increased risk for cardiovascular morbidity, but "nontreatment" would also imply withholding of quality of life improvement due to reduced hypersomnolence in these patients.

Patients were consecutively recruited based on a diagnosis of angina pectoris and/or MI and treatment in the cardiac intensive care unit. Out of 97 initially eligible patients, approximately two-thirds remained to be studied after a substantial follow-up time after the initial cardiovascular event leading to hospitalization. Although this may have lead to a negative bias excluding the patients with the most severe CAD, the approach was selected in order to avoid unintentional inclusion of patients with chronic heart failure (CHF) and potentially central apnoeas [6]. Data for left ventricular dimensions and ejection fraction were not complete. Available data included measurements made during the intensive care period and was therefore not considered to be representative of cardiac structure and function at the time of the sleep study (4–21 months after discharge from the intensive care unit). Despite seven patients demonstrating a combination of central and obstructive apnoeas, only two were classed with OSA according to the RDI definition used above. At the time of the sleep study, ongoing pharmacological treatment with nitrates, calcium antagonists, angiotensin converting enzyme-inhibitors and diuretics were more common in CAD patients with OSA compared to the patients without OSA, suggesting a possible relationship between OSA and the development of CHF in CAD patients. Regarding the functional class of the patients according to NYHA criteria, as well as an absence of dominating central apnoeas, these drugs may also reflect an optimal treatment of CAD in this population at the time of the sleep study. In other words, CHF is an unlikely explanation for an increased prevalence of OSA in CAD patients in the present study. Finally, patients included in this study had no history of neurological disorders including previous stroke, that could have influenced the prevalence of obstructive or central apnoeas [16].

Symptoms suggestive of OSA were evaluated in all subjects. The major proportion of control subjects were found to be asymptomatic. However, it is likely that symptom scores traditionally used to identify OSA syndrome are less useful in this particular population of CAD patients for several reasons. Most importantly, symptoms suggestive of excessive daytime tiredness may be related to OSA or CAD. Different pharmacological agents used in the patient group may also have influenced the frequency of such reported symptoms.

Regarding the diagnosis of OSA, all patients and controls underwent a full night of sleep/ventilatory monitoring in an identical manner. The SCSB method to record respiratory and body movements in combination with the monitoring of a BCG and S_{a,O_2} was shown to have a high validity in the detection of OSA [21] as well as central apnoeas [12].

The impact of potential confounders was carefully controlled for, as discussed in detail above. In the subsequent analysis, OSA as well as current smoking and diabetes mellitus were found to be independently associated with CAD while hypertension and hypercholesterolemia were not. As for hypertension, at least two potential explanations may be considered. The first relates to the careful matching procedure regarding age, sex and BMI undertaken to identify the controls. Almost 30% of controls were hypertensive suggesting that there may have been an unintentional selection of hypertensives due to the high mean age, 68.7 yrs, and the high BMI, 28.3 kg·m^{-2}, in that group. In addition, pharmacological agents such as nitrates, beta-blockers, calcium antagonists and angiotensin converting enzyme-inhibitors, which were used to treat CAD and/or CAD-related complications such as cardiac failure in the patient group, may certainly have resulted in a blood pressure reduction and thereby a lower than expected prevalence of untreated hypertension among patients. The high prevalence of hypercholesterolemia among both CAD patients and control subjects may also be related to the matching procedure as mentioned above. The occurrence of a positive smoking history did not differ significantly between groups but the rate of current smoking was very low (3/62) in the control group. This may reflect a lower likelihood of being a current smoker and at the same time "still healthy", in these age- and BMI-matched groups. WETTER *et al*. [22] reported an independent association (OR 4.4) between current smoking and OSA in the Wisconsin sleep cohort study, and current smoking may have been expected to favour a diagnosis of OSA in the present study. However, current smoking was found to be more common in the non-OSA group in the present CAD population. Another possible confounder might be the presence of chronic obstructive pulmonary disease (COPD) causing more pronounced oxygen desaturations during sleep. In fact, only two patients in the non-OSA group and none in the OSA group had a documented diagnosis of COPD. Although any such association between COPD and OSA may have been masked by the low absolute number of patients studied, it may be asserted that neither current smoking nor COPD is likely to have favoured the diagnosis of OSA in the present study.

Assuming OSA precedes CAD, the association between OSA and CAD may be explained by several mechanisms.

Repeated nocturnal hypoxaemia and sympathetic activation as two important consequences of apnoeas may play an important role in the development of atherosclerosis [23]. Endothelium-dependent vascular relaxation in patients with OSA was shown to be reduced independently of hypertension, which may reflect a pathogenic link between OSA and cardiovascular dysfunction [24]. The immediate and profound effects of upper airway obstruction, including hypoxaemia, changes in heart rate and blood pressure, altered cerebral blood flow, and intrathoracic pressure fluctuations, all provide multiple possible pathophysiological mechanisms for producing cardiovascular dysfunction [15]. It has also been reported that morning plasma fibrinogen concentration is increased in patients with OSA, which suggests that abnormal clotting mechanisms may contribute to an increased risk of cardiovascular events [25]. Moreover, there is evidence that episodes of OSA and oxygen desaturation lead to nocturnal myocardial ischaemia, and that nCPAP treatment of OSA patients reduces such ischaemic episodes [20]. To the authors′ knowledge, however, there is no evidence that CAD as a condition, or cardiovascular drugs such as beta-blockers taken by CAD patients, cause OSA.

In summary, these data suggest a high prevalence of obstructive sleep apnoea in middle-aged and elderly patients with coronary artery disease. The independent association between obstructive sleep apnoea and coronary artery disease, even after adjustment for traditional confounders, suggests that, obstructive sleep apnoea should be taken into account when considering risk factors for coronary artery disease, as obstructive sleep apnoea can easily be diagnosed, and in many cases represents a readily treatable condition [26, 27].

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