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Cardiovascular risk factors in patients with obstructive sleep apnoea syndrome

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ABSTRACT: Cardiovascular disorders are common in patients with obstructive sleep apnoea syndrome (OSAS) but there is debate as to whether OSAS is an independent risk factor for their development, since OSAS may be associated with other disorders and risk factors that predispose to cardiovascular disease.

In an effort to quantify the risk of OSAS patients for cardiovascular disease arising from these other factors, the authors assessed the future risk for cardiovascular disease among a group of 114 consecutive patients with established OSAS prior to nasal continuous positive airway pressure therapy, using an established method of risk prediction employed in the Framingham studies.

Patients were 100 males, aged (mean±SD) 52±9.0 yrs, and 14 females, aged 51±10.4 yrs, with an apnoea/hypopnoea index of 45±22·h^{-1}. Based on either a prior diagnosis, or a mean of three resting blood pressure recordings >140 mmHg systolic and/or 90 diastolic, 68% of patients were hypertensive. Only 18% were current smokers, while 16% had either diabetes mellitus or impaired glucose tolerance, and 63% had elevated fasting cholesterol and/or triglyceride levels. The estimated 10-yr risk of a coronary heart disease (CHD) event in males was (mean±SEM) 13.9±0.9%, 95% confidence interval (95% CI) 12.1–16.0, and for a stroke was 12.3±1.4%; 95% CI 9.4–15.1, with a combined 10 yr risk for stroke and CHD events of 32.9±2.7%; 95% CI 27.8–38.5 in males aged >53 yrs.

These findings indicate that obstructive sleep apnoea syndrome patients are at high risk of future cardiovascular disease from factors other than obstructive sleep apnoea syndrome, and may help explain the difficulties in identifying a potential independent risk from obstructive sleep apnoea syndrome.
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Obstructive sleep apnoea syndrome (OSAS) is a common disorder with a reported prevalence of 1–4% of the adult male population depending on the diagnostic criteria used [1]. The condition has been reported to be associated with a significant morbidity and mortality, particularly related to cardiovascular diseases such as heart attack and stroke [2, 3], although reports have provided different conclusions as to whether OSAS is an independent risk factor for these disorders over and above other potentially confounding variables [4–7]. However, patients with OSAS have been reported to be at increased risk of other diseases, which may also contribute to cardiovascular morbidity such as diabetes mellitus [8], thyroid disorders [9], and hypertension [10], in addition to having a high incidence of risk factors for cardiovascular disease such as obesity, hyperlipidaemia and male sex [11]. Therefore, it may become difficult to separate an independent cardiovascular risk of OSAS itself from that associated with these other comorbid factors. These difficulties have been underlined by a recent systematic review of the literature by WRIGHT *et al.* [6] who challenged the view that OSAS is an independent risk factor for cardiovascular morbidity and mortality.

No previous report has established a prediction of future cardiovascular morbidity and mortality in patients with OSAS based on coexisting risk factors for cardiovascular disease other than OSAS. The current authors performed such an evaluation in a group of consecutive patients with established moderate to severe OSAS prior to nasal continuous positive airway pressure (NCPAP) therapy using an established method of risk prediction employed in the Framingham studies [12–15]. The principal study aim was to quantify the cardiovascular risk of these patients from comorbid disease, and in particular, the study was not designed to identify an independent cardiovascular risk from OSAS itself.

Methods

One hundred and fourteen consecutive newly-diagnosed OSAS patients admitted to St. Vincent's University hospital (Dublin, Ireland) over a 15 month period for initiation of NCPAP therapy were included in the study. All patients had been referred from primary care or hospital-based physicians. All baseline data were recorded prospectively and prior to commencement of NCPAP therapy, and the pattern of data acquisition was established in advance. These included weight, height, body mass index (BMI), blood pressure, fasting total cholesterol, triglycerides and glucose levels, and 12 lead electrocardiography (ECG). Previously diagnosed medical conditions were recorded from case notes, referral letters and patient interview. Fasting blood samples were drawn for laboratory assay of total cholesterol, triglycerides and glucose and oral glucose tolerance tests were administered as necessary where borderline or mildly elevated blood sugar levels were found.

The diagnosis of OSAS was based on full polysomnography (PSG) in 99 patients, using standard criteria, and by limited overnight sleep studies using a ResMed Autoset device (ResMed PLC, Sydney, Australia), set in the diagnostic mode, in the remaining 15 patients [16]. The study population did not include any patients with central sleep apnoea or Cheyne-Stokes respiration, and all diagnostic studies were performed in this centre. Minimum nocturnal oxygen saturation was recorded from a digital oximetry probe during overnight full PSG studies (Oxford Medilog SAC 847^{TM}; Oxford Instruments PLC, Oxford, Oxfordshire, UK), and using an Ohmeda 3700e digital oximeter (Ohmeda, Louisville, CO, USA) during limited studies. The optimum NCPAP treatment pressure (in cmH_2O) was established for home use by in-hospital titration using the Autoset device (ResMed PLC).

Systolic (SBP) and diastolic (DBP) blood pressures were taken with a standard mercury sphygmomanometer with the patient seated at rest, during the first clinical assessment and subsequent recordings during the patient's hospitalization for NCPAP titration. The mean of three resting values (obtained on separate days) was used for evaluation of hypertension. Korotkoff phases 1 and 5 were used to record SBP and DBP respectively, using an appropriate sized adult sphygmomanometer cuff. Blood pressure readings were recorded to the nearest 2 mmHg. Threshold values for hypertension were defined as >140 mmHg systolic and >90 mmHg diastolic. Patients who had a diagnosis of hypertension previously established and were on antihypertensive treatment were classified as hypertensive, irrespective of current blood pressure readings.

Prospective 10-yr risk of developing a coronary heart disease (CHD) event or stroke was assessed in the study group using risk estimation methods [12–15] based on data from the Framingham study. Statistical analysis was performed using a software package (Statistica for Windows© version 4.5, StatSoft, Tulsa, OK, USA).

Results

The study population consisted of 114 patients, aged (mean±SD) 51±8.9 yrs, with a BMI of 32.9±7.9 $kg \cdot m^{-2}$, an apnoea/hypopnoea index (AHI) of 45±22 $events \cdot h^{-1}$, and minimum oxygen saturation (S_{a,O_2}) of 71±12% during sleep. These data indicate severe OSAS in the majority of patients. There were 100 males, aged 52±9.0 yrs and 14 females, aged 51±10.4 yrs. The source of referral was from General Practitioners in 68% of cases while physicians and other hospital-based specialists referred the remainder. Information regarding blood pressure and metabolic characteristics are displayed in table 1. Previously established diagnoses and those newly discovered at the time of assessment are detailed in table 2.

Table 1. – Blood pressure and metabolic characteristics of patients prior to nasal continuous positive airway pressure

	Mean±SD
Systolic BP mmHg	140±18
Diastolic BP mmHg	85±10
Fasting glucose $mmol \cdot L^{-1}$	5.9±1.4
Fasting cholesterol $mmol \cdot L^{-1}$	5.7±1.0
Fasting triglycerides $mmol \cdot L^{-1}$	2.0±1.3

BP: blood pressure.

Blood pressure

A total of 68% of patients had hypertension based on either a prior history or blood pressure recordings while in hospital. Both systolic and diastolic hypertension (SBP >140 and DBP >90 mmHg) were identified in 46% of patients, while 15.4% had isolated systolic hypertension (SBP >140, DBP <90 mmHg) and 6.7% had diastolic hypertension alone (SBP <140, DBP >90 mmHg). Only 27% of patients were already diagnosed as hypertensive and on medication prior to admission to hospital, indicating significant under-diagnosis of hypertension in this population. If higher thresholds for defining hypertension were used (SBP >160, DBP >95 mmHg), 40% of the overall patient population would still be classified as hypertensive.

Smoking history

Only 18% of patients were current smokers, although a further 45% had smoked in the past. There were no significant differences between smokers, exsmokers and nonsmokers for indices of sleep apnoea severity (AHI, continuous positive airway pressure (CPAP) or minimum overnight S_{a,O_2}) or metabolic indices, although SBP levels were higher in the exsmoker group, (147±18.2 (mean±SD, 95% confidence interval (95% CI) 141–152 mmHg), than either the current smokers, (135±16.0, 95% CI 128–143 mmHg) or the nonsmokers (13518.4, 95% CI 128–140 mmHg), p<0.05 by analysis of variance. Current and exsmokers had similar smoking histories, both in terms of pack years and daily consumption.

Table 2. – Disease prevalence in obstructive sleep apnoea syndrome patients

	Previous %	New %	Total %
DM	8.8	2.6	11.4
IGT	0.0	4.4	4.4
Hypertension	27.0	41.3	68.3
Hypothyroidism	2.6	2.6	5.2
Cardiac disease	11.4	-	11.4

Diagnoses established prior to admission (Previous); during hospitalization (New); and total prevalence (Total), expressed as percentage of whole group (n=114). DM: diabetes mellitus; IGT: impaired glucose tolerance. Cardiac disease consisted of ischaemic heart disease, cardiomyopathy and arrhythmias.

Other comorbid disease

Diabetes mellitus and hypothyroidism were relatively common (table 2) and of particular note is that approximately half of these patients were identified only at the time of OSAS assessment. Diabetes mellitus was confirmed in 13 patients (11.4%) and impaired glucose tolerance in a further five patients (4.4%). Significant correlations were found between fasting glucose and body mass (r=0.34, p<0.0005) and fasting triglycerides (r=0.33, p<0.001). The prevalence of abnormal lipid profiles is displayed in table 3, which demonstrates that >60% of patients had either high fasting cholesterol or triglycerides.

Assessment of cardiovascular risk

The risk of developing a CHD event or stroke over the next 10 yrs was assessed from the available data (age, gender, blood pressure, total cholesterol, smoking habit, ECG data and presence of diabetes mellitus) for each patient. High density lipoproteins (HDL) were not routinely measured and were not entered into the risk prediction model, so the results may tend to underestimate the true CHD risk related to abnormal lipids. The range of possible HDL cholesterol levels assessed in the model is 0.6–2.5 mmol·L^{-1}, and in the absence of HDL cholesterol data, the risk contribution to the model is assumed as zero, which corresponds to an HDL level of 1.2–1.3 mmol·L^{-1}, a level that is quite similar to values found in large scale studies among OSAS patients [11]. Exsmokers were regarded as nonsmokers for assessment by this model. The other assumptions used in these models are reported elsewhere [12–15].

The estimated 10-yr mean±SEM risk of a CHD event was 13.4±0.9%, (95% CI 11.6–15.1%) in the group as a whole. For the 100 males the predicted CHD risk was 13.90.9% (95% CI 12.1–16.0), compared to a risk of 9.2±1.5% (95% CI 4.9–11.9%) in the 14 females. When total population of 114 patients was stratified into three equally sized groups according to AHI levels (table 4), CHD risk was not significantly different between groups. Both current (mean risk 14.3±1.8%, 95% CI 10.6–18.1%) and exsmokers (mean risk 16.5±1.5% 95% CI 13.1–19.3%) had a higher 10-yr CHD risk than nonsmokers (mean risk 10.1±1.4%, 95% CI 7.2–13.0%); p<0.05.

The prospective risk of stroke estimated from the Framingham model can only be calculated for subjects aged ≥54 yrs [13]. The 10-yr (mean±SEM) prospective risk of stroke in males aged ≥54 yrs (n=40) was calculated to be 12.3±1.4%, 95% CI 9.4–15.1%. The mean±SEM age for this subgroup was 60.6±0.8 yrs. Combining 10-yr CHD risk and stroke data, this group had a mean±SEM 10-yr risk of either CHD event or stroke estimated at 32.9±2.7%, 95% CI 27.8–38.5%. When the authors stratified this latter group of 40 males into two equal subgroups based on an AHI above and below 41 events per hour (table 5) there was a trend towards a higher combined CHD and stroke risk for those with AHI >41, but this was not statistically significant (Mann-Whitney U-test).

There were only six females aged ≥54 yrs, which was regarded as too small a number to make any meaningful prediction of future stroke risk.

Table 3. – Lipid profiles in obstructive sleep apnoea syndrome patients

Description	%
High total cholesterol	46
High triglycerides	47
Percentage with both elevated	30
Isolated high total cholesterol only	16
Isolated high triglycerides only	17
Either high cholesterol or triglycerides	63

Percentage of study population with abnormal fasting lipid profiles. Reference ranges for St. Vincent's University hospital (Dublin, Ireland): total fasting cholesterol 3.1–5.8 mmol·L^{-1}; fasting triglycerides 0.15–1.8 mmol·L^{-1}.

Table 4. – Ten year predicted coronary heart disease (CHD) event risk stratified according to apnoea/hypopnoea index (AHI)

Mean AHI	Mean CHD risk	SEM	95% CI
22	14.1	1.5	11.1–17.1
45	13.6	1.4	10.7–16.5
70	13.3	1.8	9.7–16.9

Data are from three equal subgroups of 38 patients. 95% CI: 95% confidence intervals.

Discussion

This is the first survey of OSAS patients to examine prospective risk of coronary and cerebrovascular disease related to coexisting factors other than OSAS, and the results indicate that these patients are at high risk of future cardiovascular events from these other factors. A high prevalence of hypertension, noninsulin dependant (type II) diabetes mellitus, lipid disorders and hypothyroidism was also recorded. This risk assessment does not take into account any possible additional independent risk of cardiovascular disease related to the patients' OSAS, although it is interesting to note that when the data were stratified according to OSAS severity, increasing AHI levels were not associated with higher predicted risk from these other comorbid factors. However, quantifying the true contribution of OSAS will probably require prospective follow-up of large numbers of OSAS patients (treated and untreated)

Table 5. – Predicted 10-yr risk of coronary heart disease (CHD) events, stroke and combined risk

	Mean	SEM	95% CI
AHI <41			
CHD risk	19.3	1.7	15.8–22.8
Stroke risk	10.7	1.8	6.9–14.4
Combined	30.0	2.9	23.9–36.0
AHI >41			
CHD risk	22.5	2.5	17.3–27.7
Stroke risk	13.9	2.2	9.3–18.4
Combined	36.4	4.4	27.2–45.5

Data are in males aged ≥54 yrs, subdivided into two groups of equal size by an apnoea/hypopnoea index of 41 events·h^{-1}. 95% CI: 95% confidence interval.

and a suitably matched control population to allow for the confounding effects of other coexisting variables which predispose to cardiovascular disease. These considerations may help to explain the equivocal findings of some previous studies that have sought to establish the risk of cardiovascular disease in OSAS [4, 6, 7].

The relatively frequent occurrence of a wide variety of potentially confounding factors makes the selection of a suitably matched control population particularly difficult. The present study did not include a control population but this was not regarded as important since the study did not seek to identify any separate cardiovascular risk related to OSAS itself. However, the authors recognize that the patients' OSAS may have contributed to the development of some of these comorbid factors, particularly hypertension, and thus the authors cannot say that the predicted cardiovascular risk calculated in this study is entirely separate from the risk related to OSAS. Nonetheless, the lack of difference in predicted risk when the total population was stratified according to OSAS severity (tables 4 and 5) suggests that the OSAS was not a major confounding factor in these calculations. The above limitations need to be taken into account in the interpretation of the present data, but nonetheless should not detract from the core conclusion of the study which is that OSAS patients are already at high risk of cardiovascular disease from other comorbid disease, and that studies which seek to identify an independent cardiovascular risk from OSAS must take these other variables into account in their assessment.

A potential criticism of the present study is that it provides no particular insight into any independent risk factor for cardiovascular disease related to OSAS itself, even when the patient population was stratified into different subgroups based on OSAS severity. However, this was not the focus of the current study, and at a minimum, the authors believe that the findings serve two important purposes. Firstly, the data demonstrate that the predicted risk of cardiovascular disease from coexisting factors other than OSAS is high, and should provide useful baseline data to compare with other studies that evaluate cardiovascular morbidity in populations of OSAS patients, particularly where an adequate control group is not included. The findings should make one cautious in concluding that high cardiovascular risk in OSAS necessarily relates to the OSAS itself unless a suitably matched control group is compared. Secondly, by demonstrating a relatively high prevalence of other comorbid disease, the findings provide potentially useful data to help identify other factors that would need to be included in a matched control population for prospective controlled studies that seek to establish an independent cardiovascular risk related to OSAS itself. However, it is recognized that other reports have also demonstrated a high prevalence of other comorbid illness and cardiovascular risk factors in OSAS patients, but none have quantified the separate cardiovascular risk related to these factors.

Snoring and OSAS are widely reported to be associated with hypertension [17] independent of age, body weight and medications. The prevalence of hypertension in the patient population is comparable to levels described elsewhere [18], and is far in excess of the published estimated levels for similar age groups in the Irish population [19], even when threshold levels of 160 mmHg (systolic) and 95 mmHg (diastolic) are used to define hypertension. The relationship of hypertension to OSAS has not been fully clarified but activation of the autonomic nervous system by apnoeic arousals and hypoxaemia may play a role in its development [20, 21].

A number of reports have found associations of snoring and OSAS with coronary artery disease [22, 23] and with increased risk of cardiovascular death [24], although other reports disagree [25]. Mechanisms have been postulated to account for possible increased atherogenesis in OSAS [26], and it has recently been reported that patients with coexisting CHD and OSAS are at increased risk of apnoea-associated ischaemic events [27]. An association of snoring and OSAS is also reported with stroke and possibly stroke prognosis [28], though studying patients following stroke is made difficult by the fact that stroke itself may induce or worsen OSAS. The findings in this paper are in general agreement with these previous reports but do not help distinguish a separate risk from OSAS independent of other confounding variables.

One report [3] which retrospectively examined the 5-yr mortality of a cohort of OSAS patients had broadly similar baseline levels of hypertension (56.6%), age (51.34±11.3 (mean±SD) yrs), BMI (32.8±8.0 kg·m^{-2}), and OSAS severity (AHI 52.4±30.6 events·h^{-1}) as the patients in the present study. This report indicated a significantly higher death rate in conservatively managed patients (weight loss) at 11%, the majority of these due to vascular disease. The incidence of new myocardial infarction and stroke in this conservatively managed group over 5 yrs was 8.7% and 5.2 % respectively. The data concerning future cardiovascular risk related to comorbid illness are qualitatively similar when these figures are approximated to a 10-yr period, and further underline the importance of considering comorbid illness when assessing cardiovascular risk related to OSAS.

However, other reports dispute the independent association of snoring and OSAS with adverse vascular events as either unproven or of doubtful significance [6, 25, 29]. The report by WRIGHT *et al.* [6] commented that most of the existing studies were poorly designed and only weak or contradictory evidence was found of an association with cardiac arrhythmias, ischaemic heart disease, cardiac failure, systemic or pulmonary hypertension, and stroke. As many of these variables are closely inter-related, it is likely that a large scale, prospective screening and follow-up study would be required to prove the issue.

The authors estimated the predicted prospective risk of CHD events in the study population according to models based on the Framingham Study [12–14]. The mean figure of 13.4% for estimated 10-yr risk of CHD events is likely to be conservative, since the prediction model itself does not allow for possible contributing factors such as obesity and body fat distribution. The risk related to obesity may be higher in OSAS since these patients have a higher propensity to central obesity which appears to be associated with higher cardiovascular morbidity and mortality independent of BMI [30–32]. The absence of HDL data and the use of substitute neutral values of 1.2–1.3 mmol·L^{-1} may weaken the accuracy of the estimates in this study. However, large scale studies indicate that mean HDL cholesterol in patients with OSAS are quite similar to the substituted values used in the present report [11], indicating that the coronary risk estimates derived from the model are likely to be close approximations. The predicted risk of stroke is not affected by the absence of HDL data as this variable is not a factor in the stroke prediction model. The model also does not take into account factors related to OSAS itself that might contribute to CHD such as recurrent nocturnal hypoxia and inceased sympathetic drive.

As over 11% of the study population already had a diagnosis of significant overt cardiac disease (ischaemic heart disease, cardiac failure or arrhythmia) prior to the diagnosis of OSAS, their 10-yr risk of a new CHD event is probably underestimated by these prediction models. The mean 10 yr predicted risk of stroke in the study population, in male patients, at 12.3%, is higher than the predicted average for this age group [13].

The patients had relatively severe OSAS and were significantly obese as a whole. The prevalence of diabetes mellitus / impaired glucose tolerance in 16% of the patients may simply reflect the degree of obesity present in the study population [5], but the metabolic effects of increased sympathetic tone and increased circulating catecholamines due to OSAS, may also contribute to the development of diabetes mellitus. The authors found a relatively high prevalence of hypothyroidism, both established and newly diagnosed. When newly diagnosed hypothyroid patients were re-examined after being rendered biochemically euthyroid by replacement therapy, their OSAS had improved, in keeping with other reports [9], but this improvement was insufficient to discontinue NCPAP therapy. The findings suggest that specific screening for diabetes and thyroid disease is worthwhile in newly diagnosed patients with OSAS.

In summary, this report demonstrates a high prevalence of coexisting disease and cardiovascular risk factors within this patient population, and an increased risk for future adverse cardiovascular events unrelated to obstructive sleep apnoea syndrome. Since it is not known whether ongoing nasal continuous positive airway pressure treatment will reduce established risks already present, clinicians with an interest in the diagnosis and management of obstructive sleep apnoea syndrome should be aware of the prevalence of these associated conditions, and should adopt a multidisciplinary approach toward obstructive sleep apnoea syndrome patients in order to actively identify and treat these factors. Such an approach may reduce the health burden of coexisting disease and may modify the occurrence of adverse future cardiovascular events in this high-risk population.

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