

# Abstract

**Peker, Yüksel. 2000. Obstructive sleep apnea and cardiovascular morbidity.** Department of Pulmonary Medicine, Sahlgrenska University Hospital, SE-41345 Göteborg, Sweden.

Obstructive sleep apnea (OSA) affects 24 % of middle-aged men and 9 % of women in USA but the treatment criterion, daytime sleepiness is reported by 17 and 22 % of these subjects, respectively. Some previous studies have suggested an association between OSA and cardiovascular disease (CVD), but the conclusions have been conflicting due to co-existing traditionally recognized risk factors. The main aim of the present thesis was to explore the possibility of a causal link between OSA and CVD. Moreover, impact of OSA on mortality in patients with coronary artery disease (CAD) was addressed. Subsequently, long-term impact of treatment of OSA with continuous positive airway pressure (CPAP) on CVD was further explored.

In a case-control study of 62 patients with CAD requiring intensive care and 62 healthy subjects individually matched for age, gender and body-mass-index (BMI) among 571 healthy volunteers, OSA was found in 19 CAD patients and in 8 control subjects. In a multiple logistic regression analysis, OSA was significantly associated with CAD with an odds ratio of 3.1 independent of hypertension, diabetes mellitus, hypercholesterolemia and current smoking.

In a prospective study of the above mentioned clinical sample with CAD, cardiovascular death occurred in 6 of 16 OSA patients (37.5%) compared with in 4 of 43 non-OSA cases (9.3%) during a follow-up period of 5 years. In a multiple regression model, Respiratory Disturbance Index (the number of breathing pauses and oxygen desaturations per hour) was an independent predictor of mortality after adjustment for age and other traditionally recognized risk factors.

Incidence of a CVD was explored in 175 middle-aged men with or without OSA but free of hypertension or other CVD, pulmonary disease, diabetes mellitus, alcohol dependency as well as malignancy at baseline. During a follow-up period of 7 years, at least one CVD diagnosis was recorded in 21 of 37 cases (56.8%) with incompletely treated OSA compared with in 1 of the 15 efficiently treated OSA subjects (6.7%) and in 8 of 123 (6.5%) subjects without OSA. In a multiple logistic regression model, incompletely treated OSA was associated with an 11-fold increase in risk for incidence of CVD, independent of age, BMI, blood pressure and current smoking.

A retrospective study addressed the need for acute hospitalization two years prior to and two years following the initiation of CPAP treatment in OSA patients with co-existing CVD. The total number of in-hospital days was reduced from 413 to 54 in 19 CPAP-users, while in 12 non-users there was an increase from 137 to 188 days. A potential mechanism behind the beneficial effects of CPAP on cardiovascular morbidity was addressed in a separate experimental protocol. An enhanced vasoconstrictor response to angiotensin II (AT<sub>2</sub>) in the forearm arterial bed has previously been demonstrated in 10 normotensive men with OSA. Compliance with CPAP treatment (n=6) led to a significant reversal of the constrictor response, while it remained enhanced in the four non-CPAP-users.

This work supports an independent causal relationship between OSA and CVD. Moreover, OSA is associated with an increased risk of mortality in patients with CAD independent of age and traditionally recognized risk factors. CPAP treatment of OSA reduces the need for acute CVD-related hospital admissions and offers favorable cost-benefit. The treatment related reversal of the enhanced vascular response to AT<sub>2</sub> after CPAP suggests that mechanisms related to the renin-angiotensin-system play an important role in the development of CVD in OSA. These studies propose that OSA should be treated not only to eliminate daytime sleepiness. Treatment may also have a beneficial prognostic impact by reducing cardiovascular morbidity in sleep apneics.

**Key words:** Obstructive sleep apnea, cardiovascular, hypertension, coronary artery disease, hospitalization, cost utility, morbidity, mortality, secondary prevention, angiotensin II, CPAP.

**ISBN 91-628-4550-0, Göteborg, 2000**