Study Protocol

Cardiovascular effects after CPAP withdrawal for obstructive sleep apnea

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Background

Sleep apnea is common in the population and in a newly published population study of 400 women we found that 50% of them had sleep apnea and 20% had moderate and severe sleep apnea (1). More than 30,000 people in Sweden are being investigated per years for sleep apnea. The most common and effective treatment is CPAP (2-4). Many people use CPAP all and whole nights while others sometimes sleep without CPAP one or a few nights a week. However, it has not been studied whether it is dangerous to sleep without CPAP for a few nights.

Blood pressure and heart rate rise due to a stress surge and oxygenation drops during an obstructive apnea. Patients with obstructive sleep apnea are at increased risk of cardiovascular disease such as hypertension, myocardial infarction, stroke and premature death (5-6). We have previously shown that nocturnal angina is triggered by obstructive sleep apnea (7). Systemic inflammation and impaired blood vessel function including endothelial function are also associated with obstructive sleep apnea (8).

The arterial stiffness of the central arteries is mainly determined by the compliance of the aorta and increases with an impaired function of elastic fibers. Arterial stiffness increases with age, diabetes mellitus, inflammation, hypertension, obesity, smoking, cholesterol levels and atherosclerotic disease (9). Increased arterial stiffness is an independent risk factor for morbidity and death in cardiovascular disease (10). Arterial stiffness measurement is a validated and widespread method to assess endothelial function.

Many patients sometimes sleep without their CPAP. It is important from a clinical point of view to know if the cardiovascular system is affected by CPAP withdrawal for some nights.

Aims

The primary aim was to investigate the cardiovascular effects of short-term CPAP withdrawal for five nights in women and men with obstructive sleep apnea.

Design

Randomized, parallel controlled trial

Inclusion Criteria

Men and women aged 18 years old with moderate to severe obstructive sleep apnea and successful CPAP treatment for 2 months to 2 years with good compliance (mean CPAP use of >4 hours/night) during the last month before inclusion. Signed written consent to participate in the study.

Exclusion Criteria

Apnea hypopnea index >10 with CPAP treatment, heart infarction within 3 months prior to study participation, severe dementia, determined by study personal having psychological or physical hinder to participate in the study

Randomization
50 patients are randomized to sleep 5 days without CPAP and 50 patients to continue with CPAP treatment during the trial. Randomization is done by a person outside the study.

Primary outcomes
Arterial stiffness measured with pulse wave velocity, and 24-hour blood pressure.

Secondary outcomes
Effects of gender on outcome. Effects on brain natriuretic peptide, apnea-hypopnea index, oxygen desaturation-index, urine-catecholamines, blood lipids, C-reactive protein, glucose metabolism (S-glc, HBA1c), serum-insulin, serum creatinine, hemoglobin, daytime sleepiness (ESS, KSS), lung function (FVC, FEV1), airway inflammation (exhaled NO) Procedures: Sleep apnea investigation while patients are treated with CPAP for one night. Urinary samplings during the same night. They are also investigated with 24 h blood pressure measurements. Blood samples are taking fasting in the morning followed by measuring the arterial stiffness (Vicorder, Skidmore Medical UK) including pulse wave analysis using sphygmomanometer (Omron Japan). The same investigations are done at follow-up 5 days later where half of the patients have continued using CPAP treatment and half of them has slept without CPAP.

Power calculation
It was estimated that 90 patients, 45 in each group, would be needed to detect a mean (SD) blood pressure difference of 3 (5) mm Hg with a power of 80% and a significance level of 5%. It was estimated that 34 patients, 17 in each group, would be needed to detect a mean (SD) difference of 1 (1) m/s in pulse wave velocity with a power of 80% and a significance level of 5%.

Procedures
100 patients fulfilling inclusion criteria are invited to the trial after informed consent for baseline and follow-up investigations.

Baseline investigations Day 1 Patients are given a questionnaire. They are given blood pressure monitoring, (ABPM Medical 90217 ambulatory blood pressure monitor, Spacelab) for 24 hours a starting at 8-9 AM. They are also given sleep apnea investigation equipment (Embletta, X 10 system, Embla systems, ResMed) for ambulatory use during the following night, and a container for urinary sampling during the night for measurements of urine norepinephrine.

Day 2 Fasting on arrival. Return of the 24-h blood pressure recording, the sleep apnea recording and the urine sampling container.

Blood samples at 08.15 am after resting for 15 minutes. Arterial stiffness is measured using arterial pulse wave velocity, radial artery applanation tonometry and office blood pressure. After resting, the measurements start at 8.30 AM in a room with a temperature of 24°C. Pulse wave velocity (Vicorder, Skidmore Medical, Bristol, UK) is measured in the supine position. The augmentation index is derived from pulse wave

analysis obtained from radial artery applanation tonometry on the right arm (SphygmoCor, AtCor Medical, Sydney, Australia).

Lung function and exhaled NO measurements, ECG. Breakfast at around 10.00 am. CPAP time counter check Patients are then randomized with a ration of 1:1 to continue with CPAP or not for the following 5 nights.

Follow-up measurements Day 6 They are given blood pressure monitoring, (ABPM Medical 90217 ambulatory blood pressure monitor, Spacelab) for 24 hours a starting at 8-9 AM. They are also given sleep apnea recorder (Embletta, X 10 system, Embla systems, ResMed) for ambulatory use during the following night, and a container for urinary sampling during the night (urine norepinephrine).

Day 7 Fasting on arrival. CPAP time counter check Return of the 24-h blood pressure recording, the sleep apnea recording and the urine sampling container.

Blood samples at 08.15 am after resting for 15 minutes. Arterial stiffness is measured using arterial pulse wave velocity, radial artery applanation tonometry and office blood pressure. After resting, the measurements starts at 8.30 AM in a room with a temperature of 24°C. Pulse wave velocity (Vicorder, Skidmore Medical, Bristol, UK) is measured in the supine position. The augmentation index is derived from pulse wave analysis obtained from radial artery applanation tonometry on the right arm (SphygmoCor, AtCor Medical, Sydney, Australia).

Lung function and exhaled NO measurements, ECG. Breakfast at around 10.00 am. The trials ends and patients are told to continue with CPAP as usual.

Significance
Previous studies report that CPAP treatment has a beneficial effect on arterial stiffness. It is unknown whether it is dangerous to sleep without CPAP for a few days, which many patients with obstructive sleep apnea sometimes do. We will investigate whether it is hazardous for patients to be without CPAP for a few days by examining arterial stiffness and 24-hour blood pressure after 5 nights without CPAP in a randomized controlled trial.

Ethical considerations
Blood tests on the patients and this can cause some discomfort, but all blood sampling is done by experienced staff. Measuring arterial stiffness does not cause any discomfort.

Sex perspective
Both men and women of different ages are included in the study. We aim analyze women and men in separate.

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