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Effect of CPAP on diastolic function in coronary artery disease patients with nonsleepy obstructive sleep apnea: A randomized controlled trial

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ABSTRACT

Background: Obstructive sleep apnea (OSA) has been associated with worse diastolic function in patients with coronary artery disease (CAD). This analysis determined whether continuous positive airway pressure (CPAP) treatment would improve diastolic function in CAD patients with nonsleepy OSA.
Methods: Between December 2005 and November 2010, 244 revascularized CAD patients with nonsleepy OSA (apnea-hypopnea index (AHI) ≥15/h, Epworth Sleepiness Scale [ESS] score < 10) were randomly assigned to CPAP or no-CPAP. Echocardiographic measurements were obtained at baseline, and after 3 and 12 months.
Results: A total of 171 patients with preserved left ventricular ejection fraction (≥50%), no atrial fibrillation or severe valve abnormalities, and technically adequate echocardiograms at baseline and follow-up visits were included (CPAP, $n = 87$; no-CPAP, $n = 84$). In the intention-to-treat analysis, CPAP had no significant effect on echocardiographic parameters of mild (enlarged left atrium or decreased diastolic relaxation velocity) or worse (increased E/é filling index [presumed elevated left ventricular filling pressure]) diastolic function. Post-hoc analysis revealed a significant association between CPAP usage for ≥4 h/night and an increase in diastolic relaxation velocity at 12 months' follow-up (odds ratio 2.3, 95% confidence interval 1.0–4.9; $p = 0.039$) after adjustment for age, sex, body mass index, and left atrium diameter at baseline.
Conclusions: CPAP did not improve diastolic dysfunction in CAD patients with nonsleepy OSA. However, good CPAP adherence was significantly associated with an increase in diastolic relaxation velocity after one year.

1. Introduction

Diastolic dysfunction (DD) is common in patients with coronary artery disease (CAD) and preserved left ventricular ejection fraction (LVEF) [1]. Evaluation of DD has diagnostic and prognostic value in the management of patients with CAD [2,3]. Although myocardial ischemia has been suggested to be the major mechanism behind the development of DD in CAD, concomitant conditions such as hypertension, diabetes and obesity are also proposed as contributing factors [1,4,5].

Obstructive sleep apnea (OSA) is common in patients with CAD [6], and is also associated with hypertension, diabetes and obesity [7,8]. An independent relationship between OSA and DD in sleep clinic cohorts has been reported [9–12]. Recently, we showed that OSA was associated with worse diastolic function in a revascularized CAD cohort with preserved LVEF, independent of traditional risk factors [13].

First-line treatment for moderate-to-severe OSA is continuous positive airway pressure (CPAP), which reduces daytime symptoms and improves quality of life in patients with excessive daytime sleepiness [14]. Several observational studies [15–17], and two randomized controlled trials (RCT) [18,19] have shown beneficial effects of CPAP on diastolic function in sleep clinic cohorts. However, it is unclear whether CPAP improves diastolic function in patients with CAD and concomitant OSA.

The Randomized Intervention with CPAP in Coronary Artery Disease and Obstructive Sleep Apnea (RICCADSA) trial was designed to

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investigate whether CPAP reduces the risk of the composite of repeat revascularization, myocardial infarction, stroke and cardiovascular mortality in patients with CAD and nonsleepy OSA [20]. This analysis evaluated the effect of CPAP on diastolic function in patients with CAD and nonsleepy OSA as one of the secondary outcomes in the RICCADSA trial.

2. Methods

2.1. Study design and patients

The study population has been previously described [13,20]. In brief, all revascularized CAD patients were recruited from two hospitals with training and research facilities serving a population of approximately 250,000 living in the Skaraborg County of West Götaland, Sweden. Eligible patients who gave informed consent to participate in the study were referred to the Sleep Medicine Unit for sleep studies. CAD patients with nonsleepy OSA were randomized to CPAP or no-CPAP. Those with preserved LVEF, no atrial fibrillation at baseline, and technically adequate echocardiograms at 3- and 12-month follow-up visits were included in this follow-up study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Ethics Committee of the Medical Faculty of the University of Gothenburg (approval nr 207-05; 09.13.2005; amendment T744-10; 11.26.2010; amendment T512-11; 06.16.2011). All patients provided written informed consent. The trial was registered with the national researchweb.org (FoU i Sverige – Research and development in Sweden; nr VGSKAS-4731; 04.29.2005) and with ClinicalTrials.gov (NCT 00519597).

2.2. Sleep studies

Portable cardiorespiratory polygraphy (CRPG) was performed with the Embletta® Portable Digital System device (Embla, Broomfield, CO, USA). This consisted of a nasal pressure detector using a nasal cannulae/pressure transducer system, thoraco-abdominal movement detection via two respiratory inductance plethysmography belts, and a finger pulse oximeter detecting heart rate and oxyhemoglobin saturation (SpO_2) as well as body position and movement detection. Apnea was defined as almost complete (≥90%) cessation of airflow, and hypopnea was defined as a reduction in thoracoabdominal movement of ≥50% and/or in nasal pressure amplitude of ≥50% for ≥10 s [21]. In addition, the total number of significant oxyhemoglobin desaturations (defined as a decrease of at least 4% from the immediately preceding baseline value) was scored, and the oxygen desaturation index (ODI) was calculated as the number of significant desaturations per hour of estimated sleep. Events with a ≥ 30% reduction in thoracoabdominal movement and/or with a nasal pressure amplitude of ≥30% for ≥10 s were also scored as hypopneas if there was significant oxygen desaturation (≥4%). OSA was defined as an apnea-hypopnea index (AHI) of ≥15 events/h based on total recording time. All baseline screening recordings were scored by the same observer (YP).

2.3. Epworth sleepiness scale

Excessive daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) questionnaire [22]. The ESS contains eight questions to evaluate the chance of dozing off under eight scenarios in the past month. Each item is scored from 0 to 3 (0 for would never doze, 1 for slight chance of dozing, 2 for moderate chance of dozing, and 3 for high chance of dozing). The ESS score ranges from 0 to 24. Excessive daytime sleepiness was defined as an ESS score of ≥10.

2.4. Comorbidities

Baseline anthropometrics, smoking habits, and medical histories of the entire study population were obtained from medical records after mechanical revascularization. Body mass index (BMI) was calculated by dividing body weight (kg) by height (m) squared. Obesity was defined as a BMI ≥30 kg/m^2 [23]. Data on concomitant diseases at baseline, including hypertension and diabetes, type of mechanical intervention (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]), and concomitant medications were based on self-report and/or physician diagnosis reported in patient records and/or national registers.

2.5. Group assignment, randomization, interventions, and follow-up

Group assignment was based on CRPG findings. As previously described [20], the 1:1 random assignment of patients with CAD and nonsleepy OSA was performed using a sealed envelope system with a block size of eight patients (four CPAP, four controls) stratified by gender and revascularization type (PCI or CABG). Patients allocated to CPAP were informed about the technical aspects of treatment and provided with an automatic (self-titrating) CPAP device (S8®, or S9®; San Diego, CA, USA) with a nasal or full-face mask and humidifier by trained staff at the study center. All participants assigned to CPAP were instructed to use the device at home every night for ≥4 h. They were contacted by telephone after one week and had a check-up in the clinic after 1 month, 3 months, 6 months, 1 year, and then yearly to end of the main study. Nonsleepy OSA patients who were randomized to the control group, and all patients who were obese were given advice about weight reduction as part of usual care. All patients were evaluated at 3, 6, and 12 months, and annually thereafter, and were given standard cardiology treatment by their physicians.

2.6. Adherence to CPAP

OSA patients receiving CPAP brought their device to the clinic at each scheduled follow-up visit; monitoring settings and hours of CPAP use were obtained from the device's internal clocks and recorded. In addition, pressure level, mask leak and residual AHI values were noted. All necessary adjustments of the CPAP device and mask fittings were done according to clinical routines by the sleep medicine unit staff. Patients who were unable to adhere to CPAP treatment were followed as part of the treatment arm as defined in the intention-to-treat (ITT) analysis.

2.7. Transthoracic echocardiography

Echocardiographic examinations were performed by experienced echocardiographic technicians on a cardiac ultrasound system (Vivid-7 General Electric Healthcare, Fairfield, CT). Images and cine-loops were obtained in the left lateral position at rest, from the parasternal and apical position and stored and evaluated with commercially available software program (EchoPAC General Electric Healthcare). The examinations were all evaluated by the same examiner (HG), who was unaware of the patients' clinical and sleep data during the evaluations. Two-dimensional measurements included interventricular septum thickness, left ventricular posterior wall (LVPW) thickness, and left ventricular diastolic diameter (LVDD) and systolic diameter. Relative wall thickness (RWT) was calculated as LVPWx2/LVDD. Left ventricular mass (LVM) was calculated according to the corrected formula of the American society of echocardiography and normalized for body size by the height$^{2.7}$, and expressed as LVM index (LVMI) in g/m$^{2.7}$ [24,25]. Increased LVMI was defined as LVMI ≥ 49 g/m$^{2.7}$ for men and ≥45 g/m$^{2.7}$ for women [24,25]. Based on these values, concentric hypertropy was defined as the combination of an increased RWT and an increased LVMI [24,25]. Left atrial (LA) diameter was measured on parasternal M-mode images as the linear distance between the leading edge of the posterior aortic wall and the leading edge of the posterior wall. An overall evaluation of the LVEF was performed by visual estimation and, when appropriate, by the Simpsons biplane method. Transmitral peak flow velocities in early diastole (E) and peak flow

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