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Original Article

Obstructive sleep apnea is independently associated with worse diastolic function in coronary artery disease

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ABSTRACT

Background: Diastolic dysfunction is common in patients with coronary artery disease (CAD). We hypothesize that patients with CAD and preserved left ventricular ejection fraction (LVEF) and obstructive sleep apnea (OSA) will have worse diastolic function than similar patients without OSA.
Material and methods: We analyzed sleep-study recordings and echocardiographic measurements obtained at baseline in a randomized controlled trial (RICCADSA) of revascularized patients with CAD who had LVEF of at least 50%. OSA was defined as an apnea-hypopnea-index (AHI) ≥15 events/h, and, no OSA, as an AHI <5. Worse diastolic function was defined as assumed elevated left ventricular filling pressure based on peak flow velocity in early diastole/Tissue Doppler of early diastolic ventricular filling (E/é) of >13 (or >9 in patients with an enlarged left atrial diameter [≥39 mm for women and ≥40 mm for men]).
Results: Data from 431 patients were evaluated (mean age: 63.7 ± 8.8 y; men: 82.5%; OSA: n = 331). Worse diastolic function was more common among the patients with OSA than those without (54.4% *vs* 41.0%, p = 0.019). In multivariate analysis, OSA was associated with worse diastolic function (odds ratio [OR] 1.90, 95% confidence interval [CI] 1.13; 3.18) adjusted for female sex (OR 2.28, 95% CI 1.28; 4.07), hypertension (OR 1.84, 95% CI 1.20; 2.82), and diabetes mellitus (OR 2.45, 95% CI 1.42; 4.23). Age ≥60 years, obesity, and current smoking were nonsignificant.
Conclusions: In this cohort with CAD and preserved LVEF, OSA was associated with worse diastolic function independent of the traditionally recognized risk indicators.

1. Introduction

Diastolic dysfunction (DD) is highly prevalent in patients with coronary artery disease (CAD), and is thought to play an important role in the pathophysiology of heart failure with preserved left ventricular ejection fraction (LVEF) [1]. Existing data indicate that the evaluation of DD has both diagnostic and prognostic importance in the management of CAD [2,3]. Among echocardiographic parameters, the mitral flow pattern and other indices indicating an elevated left ventricular filling pressure (LVFP) have predictive value of worse diastolic function [2,3] and future hospitalization for the treatment of heart failure [4,5]. The presence of a dilated left atrium – often the result of an elevated LVFP – predicts mortality from heart failure in patients with long-standing CAD [6]. However, conflicting data show no impact of CAD on the prognosis associated with DD [7]. The controversies within this field might be explained by other concomitant comorbidities in CAD, such as increasing age, hypertension, diabetes, and obesity, which are also associated with DD [1,8]. An influence of female sex on the development of DD has also been proposed [9,10].

Obstructive sleep apnea (OSA) is common in patients with CAD [11]; it coexists in individuals with obesity, as well as in those with hypertension and diabetes [12,13]. Although several studies of patients with OSA have shown significant associations between OSA indices and abnormalities of diastolic filling [14–17], such an association could not be confirmed in a large cross-sectional study that included 500 patients with OSA [18]. Conversely, a randomized, placebo-controlled study of selected normotensive patients with OSA and without cardiovascular disease found that continuous

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positive airway pressure (CPAP) therapy resulted in improved diastolic function [19]. The impact of CPAP treatment on reversing the functional and structural remodeling of the heart has been confirmed in other smaller studies [20–23]. To date, however, there is a lack of knowledge regarding the impact of OSA on DD in patients with CAD.

In the current cross-sectional study, we aimed to address the association between OSA and worse diastolic function in patients with CAD with preserved LVEF who had undergone revascularization procedures. We also studied the diagnostic value of plasma levels of N-terminal-prohormone of brain natriuretic peptide (p-NT-proBNP) in predicting an elevated LVFP. The study was carried out within the framework of a randomized controlled trial (Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnea [RICCADSA]), which evaluates the impact of CPAP on cardiovascular outcomes in patients with CAD and OSA [11].

2. Methods

2.1. Patient population

The study population has been previously described [11]. In brief, all consecutive patients with CAD (N = 1291) who had recently (<6 months) undergone percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in the catchment area of the Skaraborg Hospitals (Skövde and Lidköping) between September 29, 2005 and November 7, 2010 were invited to participate in the trial (Fig. 1). After we excluded 32 patients with a known OSA diagnosis, a total of 1259 subjects were eligible for participation in the study. Among those, 662 agreed to undergo an ambulatory, polygraphic, cardio-respiratory sleep study at home. For the main randomized controlled trial, 511 patients fulfilled the inclusion criteria, 505 of whom had adequate baseline echocardiogram data. Data from 441 patients with preserved LVEF (at least 50%) were chosen for the purpose of the current analysis. After excluding data from 10 subjects with atrial fibrillation, severe valve abnormalities, or both, at the time of the echocardiography, 431 patients remained as the final study population (Fig. 1).

This study complied with the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Gothenburg (approval nr 207-05; 09.13.2005). The trial was registered with ClinicalTrials.gov (NCT 00519597).

2.2. Cardio-respiratory polygraphy at home

The portable, limited sleep study was performed with the Embletta Portable Diagnostic System device (Embla, Broomfield, CO), on average, 3 months after the revascularization (median, 92 days; interquartile range: 71–120 days, without significant group differences). The study consisted of a nasal pressure detector using a nasal cannula/pressure transducer system, thoraco-abdominal movement detection through 2 respiratory inductance plethysmography belts, and a finger pulse oximeter that detected heart rate and oxyhemoglobin saturation as well as body position and movement detection. Apnea was defined as an almost complete (≥90%) cessation of airflow, and hypopnea was defined as a reduction in thoracoabdominal movement of at least 50%, a reduction in nasal pressure amplitude of at least 50% for a minimum of 10 seconds [24], reductions in both thoracoabdominal movement and nasal pressure amplitude. In addition, the total number of significant oxyhemoglobin desaturations (defined as a decrease by at least 4% from the immediately preceding baseline value) was scored, and the oxygen desaturation index was calculated as the number of significant desaturations per hour of estimated sleep. Events with a reduction in thoracoabdominal movement of at least 30% with a reduction in nasal pressure amplitude of at least 30% for a minimum of 10 seconds, or reductions in both thoracoabdominal movement and nasal pressure amplitude were also scored as hypopneas if there was significant oxygen desaturation (≥4%). OSA was defined as an apnea hypopnea index (AHI) of at least 15 events per hour of the total recording time. The same observer (YP) scored all baseline-screening recordings.

2.3. Comorbidities

Baseline anthropometric measures, smoking habits, and medical histories of the entire study population were extracted from the medical records that were transcribed at the time of the mechanical revascularization. Body mass index (BMI) was calculated according to the formula of body weight divided by height squared. Obesity was defined as a BMI ≥30 kg/m^2, and abdominal obesity was defined as Waist-Hip ratio (WHR) ≥0.9 for men and WHR ≥0.8 for women, respectively [25]. Blood pressure (BP) was measured with a sphygmomanometer after a minimum of 15 minutes of the patient resting in the sitting position and using an appropriately sized arm-cuff. Data regarding known concomitant diseases at baseline, including hypertension and diabetes, the severity of CAD, angiographic findings, and type of revascularization procedure (PCI or CABG) as well as medication use at baseline were based on a combination of self-report and physician-diagnosed conditions reported in the patient records, and national registers. Uncontrolled BP was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or both [26].

2.4. Blood sampling

All blood samples were collected in EDTA and serum tubes on the morning following the baseline sleep recordings. Fasting blood glucose levels as well as blood lipid levels were determined by standard laboratory methods. P-NT-proBNP levels were determined using the commercially available solid-phase 2-site chemiluminescent enzyme-labeled immunometric assay on an Elecsys system (Roche Diagnostics; Mannheim, Germany) on samples obtained from 2005 to 2007, and on an Immulite 2000 XPi (Siemens Healthcare Diagnostics, Cardiff, Wales) from 2008 to 2010.

2.5. Transthoracic echocardiography

Cardiac function was assessed on the same day of the study following the collection of the blood samples. Comprehensive echocardiographic examinations were performed by experienced echocardiographic technicians according to the site's clinical practice on a commercially available 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 offline examiner (HG) who was unaware of the patients' clinical and sleep data. Two-dimensional measurements included interventricular septum (IVS) thickness, left ventricular posterior wall (LVPW) thickness, and left ventricular diastolic diameter (LVDD) and systolic diameter (LVSD). Relative wall thickness (RWT) was calculated as LVPW × 2/LVDD. Increased RWT was defined as RWT ≥0.42 [27]. 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$^{2.7}$ [27,28]. Increased LVMI was defined as LVMI ≥49 g/m$^{2.7}$ for men and ≥45 g/m$^{2.7}$ for women [27,28]. Based on these values, concentric hypertrophy was defined as the combination of an increased RWT and an increased LVMI [27,28]. Left atrial (LA) diameter was