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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

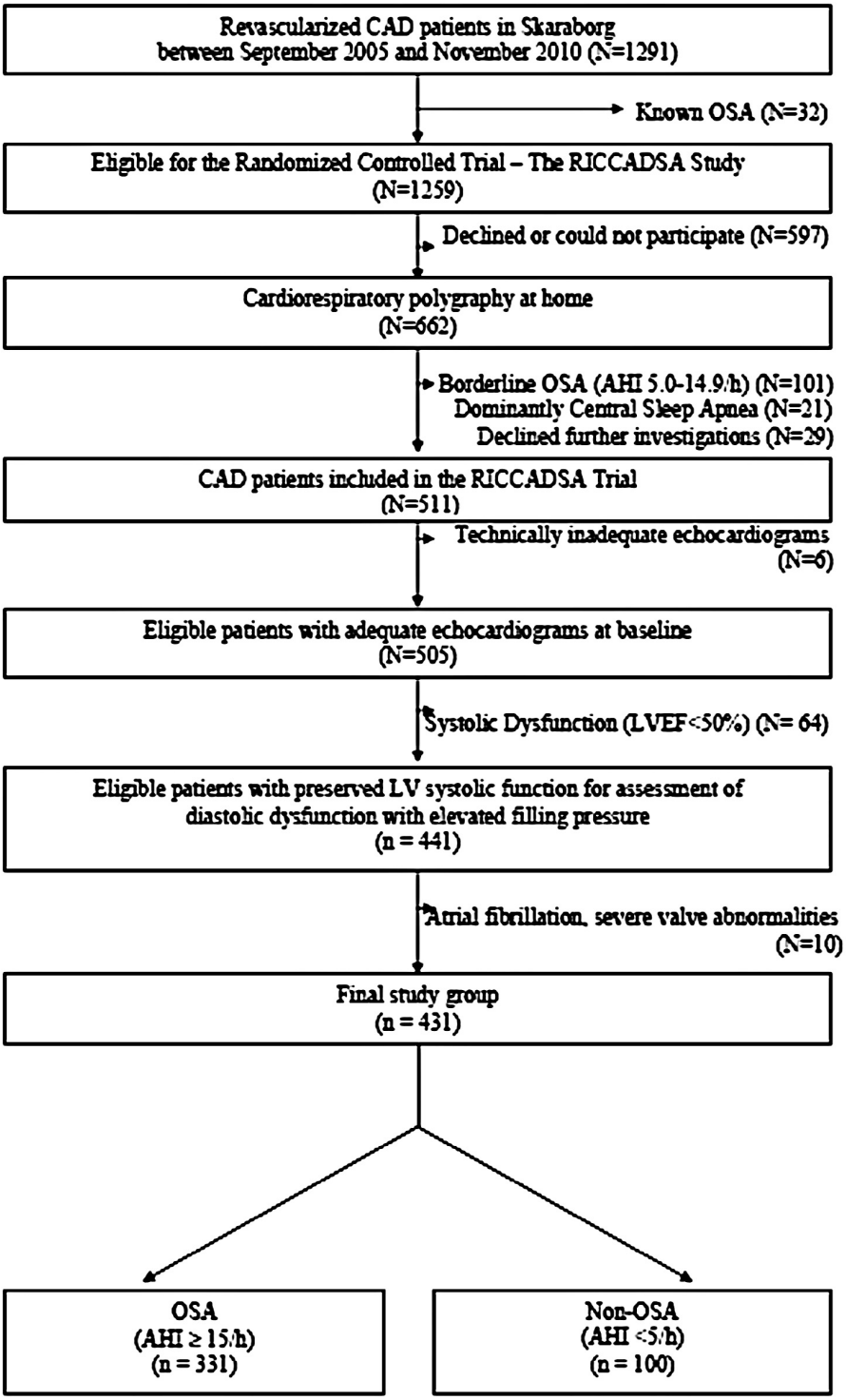

Fig. 1. Flowchart demonstrating the study cohort and the two subgroups.

measured on parasternal M-mode images as the linear distance between the trailing 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 velocity at atrial contraction (A) were recorded at the tips of the mitral valve leaflets. Peak tissue velocities were derived by pulsed tissue Doppler analysis at the septal margin of the mitral annulus for early (é) and late (á) diastolic tissue velocities, and the E/é filling index was calculated. Moreover, in case of a detectable tricuspid regurgitation, the maximum velocity in meters per second was measured with the continuous-wave Doppler, and the pressure gradient was calculated. A standardized value of 5 mmHg was then added to estimate the pulmonary artery

systolic pressure (PASP), and a PASP value >35 mmHg was defined as pulmonary hypertension [29].

Diastolic function was classified in accordance with recent recommendations with some modifications [17,27,28] as follows: (1) normal diastolic function: LA diameter was <39 mm for women, or <40 mm for men AND a normal é mean tissue velocity for age (<40 y/o: >10 cm/s; 40–59 y/o: >8 cm/s; ≥60 y/o: >6 cm/s); (2) mild diastolic dysfunction: LA diameter ≥39 mm for women, or ≥40 mm for men, OR a low é mean tissue velocity for age; and (3) worse diastolic function with a presumed elevated LVFP: E/é was >13, OR E/é > 9 in patients with an enlarged LA diameter (≥39 mm for women and ≥40 mm for men).

2.6. Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 for Windows software (SPSS Inc., Chicago, IL). For comparison of the groups, the independent sampled t-test was used. The results are presented as mean ± standard deviation. We applied the chi-squared test for comparison of the categorical variables. Interobserver variability as well as intraobserver variability for IVS, LVPW, LVDD, LA diameter, and E, A and é measurements were evaluated by the intraclass correlation coefficient (ICC) in 10% of the study population. Bivariate logistic regression was used to determine the relationship between variables associated with diastolic dysfunction with an elevated LVFP. In the multivariate regression analysis, statistically significant variables in the bivariate model, as well as the nonsignificant variables with supposed clinical relevance, were included. All odds ratios (ORs) are presented with their 95% confidence intervals (CI). All statistical tests were two-sided, and p-values less than 0.05 were considered statistically significant.

3. Results

As shown in Table 1, the patients with OSA were older, were more likely to be men, and showed more comorbidity in terms of obesity, hypertension, diabetes, and history of atrial fibrillation compared patients with CAD without OSA. The proportion of patients on β-adrenergic receptor blockers (β blockers), diuretics, and angiotensin II receptor blockers (ARBs) was also higher in the OSA group. Almost half of the CAD population has uncontrolled BP with no significant differences identified between the groups. The proportion of current smokers and patients with lung disease tended to be higher in the non-OSA group. History of myocardial infarction and stroke did not differ between the groups. Plasma levels of triglycerides were higher and high-density lipoprotein (HDL) cholesterol levels were lower in the OSA group, whereas LDL levels did not differ significantly between groups. Mean plasma levels of NT-proBNP were also higher in the OSA group. Mean AHI for the whole OSA group reflected moderate to severe OSA and patients had mild daytime sleepiness (Epworth Sleepiness Scale score <10; Table 1).

As summarized in Table 2, the patients with revascularized CAD and OSA showed significantly higher values of IVS, LVPW and RWT as well as LVMI compared with the patients with CAD but without OSA. Concentric hypertrophy based on the given criteria tended to be more common in the OSA group. LA diameter was significantly larger in the OSA group. Mean é tissue velocity and E/A ratio values were reduced in the OSA group whereas the mean E/é did not differ significantly between the groups. Among patients with detectable tricuspid regurgitation, the PASP values were significantly higher in the OSA group (Table 2). The percentage of subjects with pulmonary hypertension based on the given criteria did not differ between the groups. DD with a normal or an elevated LVFP, based on the given criteria, was more common in the OSA group, and the proportion of patients with CAD and worse diastolic function was significantly higher in the OSA group. As shown in Table 3, the

Table 1
Demographic and clinical characteristics of the patients with revascularized CAD and preserved ejection fraction.

Variable	OSA (n = 331)	Non-OSA (n = 100)	p Value*
Age (y)	64.2 ± 8.0	60.8 ± 9.6	<0.001
Age ≥60 y	68.9	58.0	0.044
AHI, events/h	29.7 ± 14.8	3.0 ± 1.3	<0.001
ESS score	8.1 ± 4.0	5.8 ± 3.0	<0.001
BMI, kg/m^2	28.9 ± 4.0	25.6 ± 2.9	<0.001
Obesity	31.4	6.0	<0.001
Abdominal obesity	94.4	79.8	<0.001
Male sex	84.3	76.0	0.057
Current smoker	16.7	25.3	0.062
Pulmonary disease	7.9	12.0	0.203
Hypertension	62.4	47.0	0.006
Uncontrolled blood pressure	48.1	45.4	0.631
History of myocardial infarction	62.6	65.0	0.665
History of atrial fibrillation	15.9	6.1	0.013
Diabetes mellitus	23.6	13.0	0.023
Stroke	5.5	3.0	0.322
Medication use			
β-blockers	90.1	81.4	0.021
Diuretic	19.5	9.4	0.021
CCB	20.4	12.4	0.073
ACE inhibitor	38.1	38.1	0.991
ARB	15.5	6.2	0.018
Lipid-lowering agent	95.4	93.8	0.522
Blood samples			
p-NT-proBNP, ng/L	345.6 ± 543.8	250.8 ± 228.4	0.012
p-Triglycerides, mmol/L	1.5 ± 0.9	1.3 ± 0.8	0.021
p-HDL cholesterol, mmol/L	1.2 ± 0.3	1.4 ± 0.3	<0.001
p-LDL cholesterol, mmol/L	2.5 ± 0.7	2.4 ± 0.7	0.934

Abbreviations: OSA, obstructive sleep apnea; AHI, apnea hypopnea index; ESS, Epworth Sleepiness Scale; BMI, body-mass-index; CCB, calcium channel blocker; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; p-NT-proBNP, plasma N-terminal-pro-hormone of brain natriuretic peptide; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

* Continuous variables are expressed as mean ± SD, others as percentages. Statistics by unpaired Student's *t* test. Comparison of groups by chi-squared test.

Table 2
Echocardiographic findings of the patients with revascularized CAD and preserved ejection fraction.

Variable	OSA (n = 331)	Non-OSA (n = 100)	p Value*
IVS thickness (mm)	13.4 ± 2.5	12.2 ± 2.5	<0.001
LVPW thickness (mm)	11.7 ± 2.1	11.0 ± 1.9	0.001
LVDD (mm)	46.9 ± 5.6	47.6 ± 6.8	0.301
LVDS (mm)	29.9 ± 5.8	30.3 ± 5.5	0.504
RWT (mm)	0.51 ± 0.12	0.47 ± 0.10	0.002
LVMI (g/m$^{2.7}$)	51.6 ± 13.0	48.0 ± 15.8	0.022
Concentric hypertrophy (%)	45.0	35.0	0.076
LA diameter (mm)	43.4 ± 5.5	40.2 ± 4.6	<0.001
é septal (cm/s)	6.8 ± 1.6	7.6 ± 1.8	<0.001
E/A (ratio)	1.0 ± 0.3	1.2 ± 0.4	<0.001
E/é (ratio)	11.0 ± 3.6	10.4 ± 3.7	0.139
LVEF (%)	60.0 ± 5.0	60.2 ± 4.3	0.743
PASP (mmHg)†	30.4 ± 5.5	28.2 ± 5.0	0.007
Pulmonary hypertension (%)†	12.9	8.1	0.312
Diastolic dysfunction (%)	92.1	83.0	0.007
Elevated LVFP (%)	54.4	41.0	0.019

Abbreviations: CAD, to coronary artery disease; LV, left ventricular; OSA, obstructive sleep apnea; IVS, interventricular septum; LVPW, LV posterior wall; LVDD, LV diameter in diastole; LVDS, LV diameter in systole; RWT, relative wall thickness; LVMI, LV mass index; LA, left atrium (M mode); é, tissue Doppler of early diastolic ventricular filling; E/A, peak flow velocity in early diastole/peak flow velocity in atrial contraction; E/é, peak flow velocity in early diastole/medial é- velocity; LVEF, LV ejection fraction; LVFP, LV filling pressure; PASP, pulmonary artery systolic pressure.

* Continuous variables are expressed as mean ± SD, statistics by unpaired Student's *t* test. Comparison of groups by chi-squared test (two tailed).

† Measurements were performed in 163 patients with OSA and 62 without OSA with detectable tricuspid regurgitation.

Table 3
Interobserver and intraobserver agreement for the echocardiographic measurements evaluated by the intraclass correlation coefficient (ICC).

Measurements	Interobserver variability	Intraobserver variability
IVS thickness	0.876	0.958
LVPW thickness	0.666	0.894
LVDD	0.953	0.990
LA diameter	0.965	0.996
E	0.985	0.993
A	0.993	0.997
é septal	0.964	0.988

Abbreviations: IVS, interventricular septum; LVPW, left ventricular posterior wall; LVDD, left ventricular diameter in diastole; LA, left atrium (M mode); E, peak flow velocity in early diastole; A, peak flow velocity in atrial contraction; é, tissue Doppler of early diastolic ventricular filling.

inter-observer concordance revealed ICCs between 0.666 and 0.993, whereas the repeated intra-observer measurements had ICCs between 0.894 and 0.997.

In a bivariate logistic regression analysis of the categorical variables, OSA, female sex, hypertension, and diabetes mellitus as well as hypertrophic remodeling and pulmonary hypertension (based on the echocardiography findings) were significantly associated with worse diastolic function, whereas age greater than 60 years, obesity, abdominal obesity, excessive daytime sleepiness, current smoking and history of atrial fibrillation were not (Fig. 2). Among medication use, β-blockers, ACE inhibitors, and ARBs were more likely to be used by those patients with worse diastolic function. There was a linear relationship between worse diastolic function and increasing cut-off levels of p-NT-proBNP. As illustrated in Fig. 3, the multivariate logistic regression analysis revealed OSA, female sex, hypertension, and diabetes mellitus as significant correlates of worse diastolic function.

The continuous variables of age, and systolic BP as well as RWT and LVMI were significantly related with worse diastolic function in the bivariate logistic regression analysis, whereas BMI, WHR, diastolic BP, AHI, Epworth Sleepiness Scale score, and PASP were not (Table 4). Among possible key mediators of the worse diastolic function tested, concentric hypertrophy, age, and systolic BP remained as significant variables in the multivariate analysis adjusted for BMI and AHI (Table 5).

4. Discussion

In this relatively large cross-sectional cohort of patients with CAD with preserved LVEF, OSA was independently associated with a worse diastolic function – an assumed elevated LVFP based on echocardiographic findings. There was an almost 2-fold increase in risk of having worse diastolic function, adjusted for the traditionally recognized risk indicators.

The results of several studies conducted during the past decade have suggested a high prevalence of DD in patients with CAD and preserved EF. Although myocardial ischemia per se in CAD has been suggested as playing an important role in DD, other comorbid conditions such as increasing age, female sex, hypertension, diabetes, and obesity have also been highlighted as risk factors [1,8,9]. However, OSA, which is highly prevalent in patients with CAD [11], and which also has been related with DD [14–17], has not previously been accounted for in CAD cohorts in this context.

In our study, we observed DD – with either a normal or an elevated LVFP – among 90% of the cohort. This is not an unexpected finding given the pathophysiologic mechanisms of DD, such as increased arterial stiffness, and myocardial hypertrophy with or without slowed or incomplete relaxation due to myocardial ischemia per se or its risk factors in CAD [1]. However, DD with an elevated LVFP, which has been shown to have an important prognostic value [4], was more common among the patients with OSA patients compared to those without OSA, in our cohort (Table 2).

Regarding the other comorbidities related with DD, studies have also shown more pronounced abnormalities of the LVM and LA remodeling in hypertensive patients [8,30]. In line with those reports, our multivariate analysis also showed that hypertension was

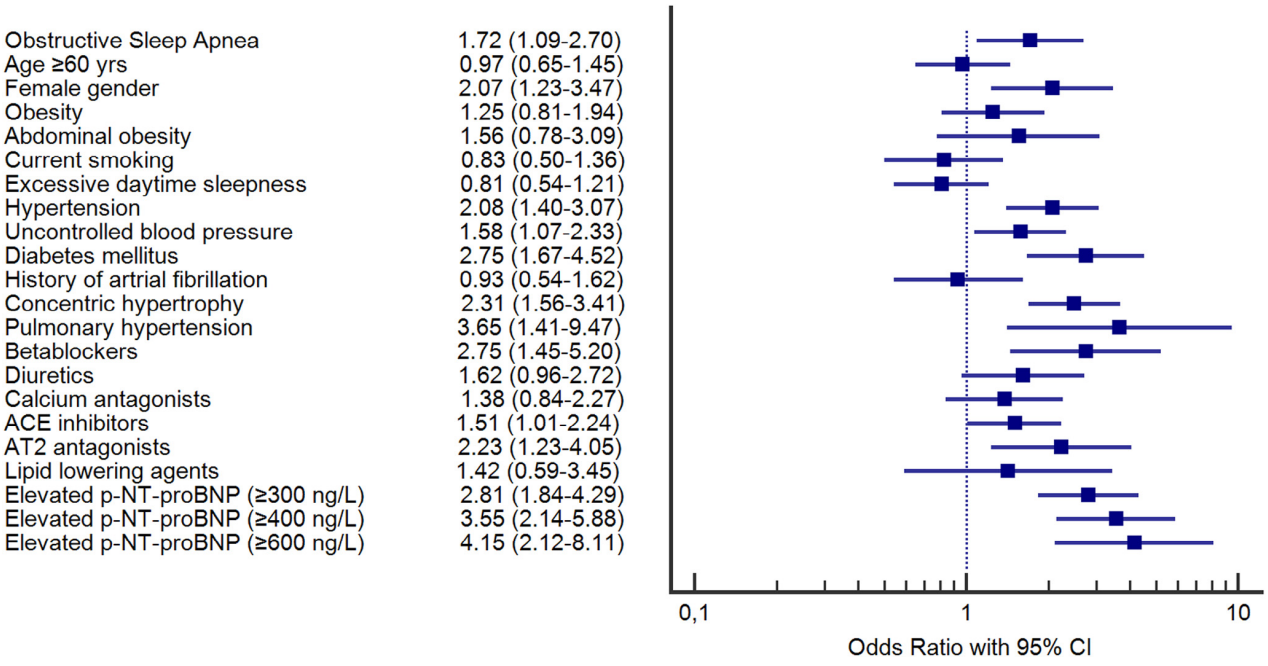

Fig. 2. Categorical variables associated with worse diastolic function in patients with revascularized coronary artery disease and preserved left ventricular ejection fraction. CI, confidence interval; ACE, angiotensin converting enzyme; AT2, angiotensin II receptor; p-NT-proBNP, plasma N-terminal-prohormone of brain natriuretic peptide.

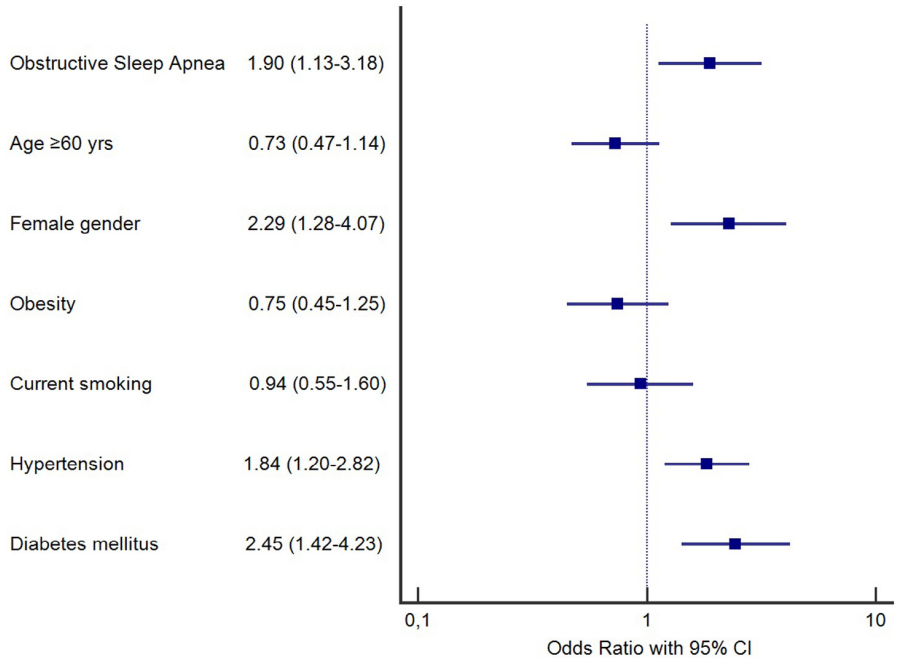

Fig. 3. Multivariate regression analysis of the clinical variables associated with worse diastolic function in patients with revascularized coronary artery disease and preserved left ventricular ejection fraction. CI, confidence interval.

associated with worse diastolic function with an OR of 1.8 in our cohort, Moreover, our results, which show an almost 2.5-fold increase in risk among the subjects with diabetes, support the findings from previous studies regarding an independent relationship between diabetes mellitus and DD [31,32]. Echocardiographic studies have shown an increased LVW thickness and an increased LVMI among patients with diabetes, even after accounting for BMI and blood pressure [33]. Evidence of diastolic filling abnormalities, even early in the course of diabetes (ie, without complications), has led to the suggestion that DD is the result of the diabetes itself [34]. The interrelationships between OSA and hypertension as well as between OSA and diabetes mellitus in our cohort introduce OSA as a new synergistic and additive factor in this context.

Women with metabolic syndrome but without diabetes and overt cardiovascular diseases have been shown to be more prone to developing DD, primarily via LV remodeling [9]. Our findings support this significant influence of sex on DD among patients with CAD. On the contrary, another report did not demonstrate significant sex differences in the relationship between metabolic syndrome and LV remodeling [10]. These conflicting results have been ascribed to the small number of patients in these studies as well as different comorbidities and medications [9]. Given the fact that not all studies applied sex-stratified cut off values in the determination of DD might be an additional explanation for these inconsistent findings.

The role of obesity in the development of DD and heart failure with preserved LVEF has been one of the most controversial issues. Though obese subjects had a 2-fold increased risk for developing heart failure in the Framingham Heart Study [35], there are also studies paradoxically showing improved outcomes among obese individuals when compared with those with normal BMI [36]. Moreover, Taylor et al. found depressed p-NT-proBNP values in obese individuals despite their having LV end diastolic pressures [37]. The complex relationship between obesity and hypertension, insulin resistance, neurohormonal activation and increased oxidative stress have all been suggested as explanatory mechanisms for the development of DD [8]. We found no association between neither obesity or abdominal obesity and worse diastolic function in our cohort, supporting the hypothesis that comorbid conditions and other pathophysiologic mechanisms, rather than obesity per se, have the major influence in this context.

Despite increased research evidence indicating that OSA may be a contributing risk factor for DD [14–17], a large cross-sectional study

Table 4
Continuous variables associated with worse diastolic function patients with revascularized CAD and preserved ejection fraction.

	OR	95% CI	p Value
Age	1.05	1.02–1.07	<0.001
BMI	1.01	0.96–1.06	0.764
WHR	0.65	0.27–1.53	0.327
Systolic BP	1.02	1.01–1.03	0.001
Diastolic BP	1.01	0.99–1.02	0.553
AHI	1.01	0.99–1.02	0.247
ESS	0.97	0.92–1.01	0.165
RWT	17.40	3.15–96.18	0.001
LVMI	1.04	1.03–1.06	<0.001

Abbreviations: CAD, coronary artery disease; OR, odds ratio; CI, confidence interval; BMI, body-mass-index; WHR, waist-hip ratio; BP, blood pressure; AHI, apnea hypopnea index; ESS, Epworth Sleepiness Scale; RWT, relative wall thickness; LVMI, left ventricular mass index.

Table 5
Sex-adjusted multivariate regression analysis of the continuous variables and concentric hypertrophy associated with worse diastolic function in patients with revascularized CAD and preserved ejection fraction.

	OR	95% CI	p Value
Concentric hypertrophy	2.19	1.43–3.34	<0.001
Age	1.04	1.02–1.07	0.001
Systolic BP	1.01	1.00–1.02	0.020
BMI	0.99	0.94–1.05	0.791
AHI	0.99	0.99–1.01	0.896

Abbreviations: CAD, coronary artery disease; OR, odds ratio; CI, confidence interval; BP, blood pressure; BMI, body-mass-index; AHI, apnea hypopnea index.

that included more than 500 patients with OSA did not find a significant relationship between OSA and DD [18]. Fung and colleagues showed that severe OSA (AHI >40 events/h) was significantly linked to diastolic abnormalities in the setting of normal LVEF [14]. Additional smaller studies in patients with OSA also showed significant associations between OSA indices and abnormalities of diastolic filling [15,16]. More recently, Wachter and colleagues addressed the prevalence and severity of DD among 352 individuals with at least 1 risk factor for DD (hypertension, diabetes, OSA, atherosclerotic disease or signs and symptoms of heart failure) recruited from a primary care population [17]. They found that moderate to severe OSA (AHI ≥15 events/h; based on cardio-respiratory polygraphy) was independently associated with DD in patients with classical risk factors for DD. Our study results, using nearly similar definitions for DD with an elevated LVFP, support this independent relationship. However, the severity of OSA in terms of AHI was not predictive for worse diastolic function in our population which had established CAD. Of note, the proportion of patients on β-blockers, diuretics, and ARBs was higher in the OSA group, reflecting higher level of or more severe comorbidities. However, given the inclusion criteria for the entire RICCADSA cohort, excluding the patients with predominantly central sleep apneas with Cheyne–Stokes respiration (Fig. 1), and further excluding patients with an LVEF less than 50%, this finding might also suggest that patients with OSA were medically better treated than were the patients with CAD without OSA. Thus, our findings are interesting given that a worse outcome may be presumed in these patients, despite being medically better treated, which further supports the concept of treating OSA to prevent future cardiac failure [23,38].

Several mechanisms might explain the independent relationship between OSA and worse diastolic function. OSA is linked to echocardiographic measurements of concentric hypertrophy [18] as well as insulin resistance, neurohormonal activation, increased oxidative stress and systemic inflammation [39], which all have been suggested as explanatory mechanisms for the development of DD. The higher prevalence of concomitant hypertension and diabetes, as well as the increased RWT and LVMI as signs of concentric hypertrophy in the OSA group in our population, may also explain the higher occurrence of DD with an elevated LVFP.

Less is known regarding the diagnostic and prognostic role of p-NT-proBNP in the evaluation of DD with an elevated LVFP. Reinhart and colleagues investigated echocardiographic measurements of LVH, atrial dilatation, and LV dysfunction and their relationship with p-NT-proBNP levels on subclinical CAD in patients with diabetes [40]. In that cohort, DD was frequently observed but no significant relationship existed between echocardiographic measurements and p-NT-proBNP levels. When we applied different cut-off values of p-NT-proBNP levels, which were suggested for patients with heart failure and preserved LVEF, we found a significant association with increasing ORs (Fig. 2). Thus, p-NT-proBNP level seems to be an important marker of DD with an elevated LVFP in patients with CAD patients and a preserved LVEF.

4.1. Limitations

One may argue that the diagnostic criteria of OSA were based on cardiorespiratory sleep studies instead of full polysomnography, and could therefore, not reflect true sleep time and arousals. However, the cut-off value for AHI (15/h) that we chose for OSA diagnosis, as well as the cut-off value (5/h) chosen for non-OSA, have both been previously shown to be reliable for the Embletta system [41] used in the current trial. Though we had obtained full polysomnographic recordings in patients with OSA before the start of the randomized controlled trial in the protocol, these investigations were planned primarily to further evaluate sleepy versus non-sleepy OSA phenotypes and address the associations with OSA severity as well as the sleep stages and worse diastolic function.

The definition and grading of DD have been extensively debated during the past few decades. One limitation of our findings was that, because of the clinical practice in our hospitals at the time of the study, which began in 2005, we relied on diameter rather than volume of the LA on echocardiography. However, we applied the recommended sex-stratified cut-off values for definition of a dilated LA [27,28]. These have been suggested to predict heart failure mortality in patients with long-standing CAD [4]. In addition, we also relied on the well-validated parameters of DD, such as tissue Doppler velocities as recommended by the current guidelines [28], which have been shown to predict future hospitalizations for the treatment of heart failure [4,5]. Though E/é alone has been shown to have limited sensitivity to identify an LVFP [42], we relied on the combination of E/é values and the enlargement of LA parameters, as was recently suggested by Wachter and colleagues [17]. Among patients with detectable tricuspid regurgitation, the percentage of subjects with pulmonary hypertension based on the given criteria was not much higher in this CAD cohort with preserved LVEF. However, pulmonary hypertension based on the echocardiography findings was significantly associated with an elevated LVFP, which is a finding in accordance with a previous report by Lam and colleagues [29].

Because this cross-sectional study did not include clinical symptoms of heart failure, our report is limited to only echocardiographic parameters of DD with an elevated LVFP. However, introducing the p-NT-proBNP-levels in combination with the echocardiographic findings may have further implications to predict prognosis in CAD.

Of note, the current report refers to baseline cross-sectional investigations of a clinical cohort, but the relationship between OSA and worse diastolic function in this CAD population may not necessarily indicate a causal association, because a primary endpoint was not defined. However, the impact of CPAP treatment on cardiac function was previously described among the secondary endpoints in the RICCADSA trial [11] and would hopefully contribute to the causality issue when the data analyses are completed within the near future.

5. Conclusion

In this cohort with CAD and preserved EF, OSA was independently associated with worse diastolic function, as evidenced by signs of an elevated LVFP, independent of the traditionally recognized risk indicators. These new findings in a well-defined cohort of patients with CAD, which had not previously been investigated with respect to the association between OSA and DD, corroborate previous reports from sleep clinic and primary care cohorts [14–17]. Concentric hypertrophy seems to be a key mediator of the concomitant effect of aging, hypertension, diabetes, and OSA into worse diastolic function. However, whether CPAP treatment of OSA in this population with high-risk comorbitites but optimal medical treatment improves diastolic function and prevents future cardiac failure remains to be seen.

Conflict of interest

Helena Glantz, Erik Thunström, Magnus C Johansson, Cecilia Wallentin Guron, Harun Uzel, Jan Ejdebäck, and Salmir Nasic report no conflict of interest. Yüksel Peker has received institutional grants from ResMed, and Bioprojet, and consulting and lecture fees from ResMed.

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