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Impact of obstructive sleep apnea on diastolic function

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Abstract

We investigated whether OSA independently affects diastolic function in a primary care cohort of patients with cardiovascular risk factors.

378 study participants with risk factors for diastolic dysfunction (DD) were prospectively included and a polygraphy was performed in all patients. DD was assessed by comprehensive echocardiography including tissue Doppler. Sleep apnea was classified according to apnea/hypopnea index (AHI) as none (AHI <5), mild (5 ≤ AHI < 15) or moderate/severe (AHI ≥ 15/h).

Patients with central sleep apnea (n=14) and patients with previously diagnosed sleep apnea (n=12) were excluded. In the remaining 352 subjects, 21.6 % had an AHI ≥ 15/h. The prevalence of DD increased with the severity of sleep apnea from 44.8 % (none) to 56.8 % (mild) to 69.7 % (moderate/severe sleep apnea), p=0.002. The degree of DD also increased with sleep apnea severity (p=0.004). In univariate regression analysis, age, desaturation index, AHI, heart rate, AT1 receptor antagonist therapy, body mass index and left ventricular mass were associated with DD. In multivariate regression analysis, only age, BMI, AHI and heart rate were independently associated with DD.

Moderate/severe obstructive sleep apnea is independently associated with DD in patients with classical risk factors for diastolic dysfunction.

Keywords: Sleep apnea; diastolic function; echocardiography

Introduction

Chronic heart failure (CHF) is a substantial, still growing epidemic burden for western societies[1]. About half of the patients presenting with the clinical syndrome of heart failure have a normal left ventricular ejection fraction[2,3]. These cases are defined as "Heart failure with preserved ejection fraction" (HFprEF) and left ventricular diastolic dysfunction is considered to be a common underlying pathology[4]. HFprEF typically occurs in the elderly and is associated with classical risk factors such as arterial hypertension[5], diabetes mellitus[6] and atrial fibrillation[7]. The prognosis of HFprEF patients, once hospitalized for heart failure, is similarly poor as in heart failure with reduced ejection fraction, but has, in contrast to heart failure with reduced ejection fraction, not improved during the last decades[2,3]. Convincing therapeutic strategies for HFprEF other than risk factor control are lacking.

In recent years intensive research has revealed multiple negative consequences of obstructive sleep apnea (OSA) on the cardiovascular system[8,9]. The pathophysiologic interaction between OSA and cardiovascular disease is complex and comprises sympathetic activation, inflammation, oxidative stress, endothelial dysfunction and clock gene dysfunction[9,10,11]. OSA is an independent risk factor for arterial hypertension[12,13,14]. Epidemiologic data demonstrate that OSA has prognostic implications for cardiovascular morbidity and mortality (for review see[8]). Uncontrolled studies indicate that OSA therapy improves this elevated cardiovascular risk[9].

Furthermore, in a randomized, placebo controlled, double blind study in selected normotensive OSA patients without cardiovascular disease CPAP therapy resulted in improved diastolic function[15]. The potential of CPAP therapy to reverse functional and structural remodelling of the heart has been confirmed in several studies[16,17,18,19]. However, it is currently unclear whether OSA is an independent risk factor for diastolic dysfunction and diastolic heart failure. Smaller studies in OSA patients revealed that oxygen desaturation[20,21] or obstructive apneas[22] were associated with abnormalities of diastolic filling. However, such

an association could not be confirmed in a large cross sectional study including over 500 patients with OSA[23].

We hypothesized that hitherto undiagnosed obstructive sleep apnea is independently associated with diastolic dysfunction. Therefore, we assessed sleep breathing patterns and diastolic function in a large, prospective cohort of non-cardiac primary care patients with cardiovascular risk factors.

Methods

Subjects

Patient recruitment has previously been described in detail[6]. The German competence network heart failure (www.knhi.de) is a publicly funded multicenter initiative for heart failure research. We recruited a total of 1732 General Practitioners´ (GP) patients at risk for heart failure (AHA/ACC stage A or B) or with signs/symptoms of heart failure (stage C) into the prospective longitudinal DIAST-CHF study, which is part of the network.

Inclusion criteria were both of the following:

(1) Age 50 to 85 years

(2) At least one risk factor for diastolic dysfunction (hypertension, diabetes, sleep apnea, atherosclerotic disease, signs/symptoms of heart failure)

The only exclusion criteria were inability to participate or consent or severe concomitant diseases.

Patients with heart failure were also included as part of the inclusion criteria of DIAST-CHF. As the impact of sleep apnea may vary in patients with and without heart failure, analyses were repeated after exclusion of heart failure patients (see results).

Candidates were identified by a software-based search strategy of the patient databases of participating GP´s computer systems. Suitable patients were invited to participate by their GP. All those who consented (52 %) underwent a comprehensive non-invasive diagnostic workup at baseline, including patient history and physical examination, laboratory analyses, ECG, bodyplethysmography, comprehensive echocardiography, 6 min walk test and several psychosocial and quality of life questionnaires.

A substudy with polygraphy was offered to participants at the study site Göttingen. These participants were randomly selected from the total local cohort (first patient per day).

The study complies with the Declaration of Helsinki, the protocol was approved by the responsible ethics committee and all patients gave written informed consent.

Polygraphy

Over an inclusion period of 18 months, ambulatory investigation for sleep disordered breathing was performed with the Stardust II Sleep recorder (Philips Respironics, 5680 DA Best, The Netherlands) as published previously[24]. The median time between the echocardiographic examination and the sleep recorder study was 11.5 days [6 days; 29 days]. Oxygen saturation and heart rate were recorded by fingertip pulse oximetry. Airflow was monitored by nasal pressure, while thoracic wall motion was measured by an inductive plethysmographic belt tightly wrapped around the chest. Analysis was conducted manually by two of the investigators (LL and DK) blinded to the patient's echocardiographic and laboratory data using custom-software provided by the manufacturer. Respiratory events needed a minimum duration of 10s for analysis. An apnea was considered obstructive when nasal flow was absent in the presence of thoracic movements, and central when movements were absent as well. Hypopneas were defined as a 50% or greater reduction in tidal volume and a ≥3% desaturation from the baseline value as compared with the preceding signals. Based on the apnea/hypopnea index (AHI) for time in bed (recording time), patients were classified into 3 groups:

A: no sleep apnea (AHI < 5/h)

B: mild sleep apnea (AHI 5-14/h)

C: moderate/severe sleep apnea (AHI ≥15/h)

Echocardiography

Comprehensive echocardiography including careful evaluation of diastolic function was performed on a Hewlett-Packard Sonos 5500 (Hewlett-Packard, Andover, MA, USA) according to the guidelines of the American Society of Echocardiography (ASE). Briefly, transmitral peak velocities of early (E) and late or atrial (A) inflow and E wave deceleration

time were recorded at the tips of the mitral valve leaflets. Isovolumetric relaxation time (IVRT) was obtained in the apical five chamber view. Peak tissue velocities were derived by tissue Doppler analysis at the medial and lateral margin of the mitral annulus for early (e´) and late (a´) diastolic inflow. E/e´ was calculated using the mean of medial and lateral e´. Left atrial volume was calculated by the ellipsoid formula as previously described[25] and left atrial volume index (LAVI) was calculated as left atrial volume indexed to body surface area. LV end-diastolic and end-systolic volumes (LVEDV and LVESV) and LV ejection fraction (EF) were measured by the modified Simpson´s method. LV mass (LVM, g) was calculated by the Devereux formula[26] and was normalized for body surface area and additionally expressed as LVM Index (LVMI, g/cm^2).

Diastolic dysfunction was classified according to recent recommendations[27] as follows:

- Normal diastolic function (e´ (lateral) > 10 cm/s, e´ (medial) > 8 cm/s, LAVI < 34 ml/m².
- Mild diastolic dysfunction (E/A < 0.8, e´ (lateral) < 10 cm/s, e´ (medial) < 8 cm/s).
- Diastolic dysfunction with elevated filling pressures (E/e´ > 13 cm/s or (E/e´ > 9 and LAVI > 34 ml/m²))

Diastolic function could not be classified in two study participants with atrial fibrillation who fulfilled neither the definition for normal diastolic function nor for diastolic dysfunction with elevated filling pressures, because mild diastolic dysfunction could not be diagnosed because of a missing A wave in atrial fibrillation.

Calculations and Statistical Analyses

Data are presented as mean ± SD, if variables were normally distributed. Variables not normally distributed are expressed as median [interquartile range] for continuous variables or absolute number (percentage) for categorical variables. Continuous data were compared by ANOVA (followed by Tukey´s post hoc test) or Mann-Whitney U-test, categorical data were compared by chi-square or Kruskal-Wallis test.

To assess the association between two continuous variables, bivariate correlation analysis was used. To analyse which variables are associated with diastolic dysfunction, univariate analyses were performed separate for each variable using binary logistic regression analysis. The variables that showed a statistically different baseline characteristic between no OSA and the OSA groups or which have been described in the literature as causes of diastolic dysfunction were included in the analysis. Variables with a probability value ≤ 0.10 in univariate analyses or well known causes of diastolic dysfunction were candidates for multivariable logistic regression analysis with stepwise-inclusion ($p<0.05$ for entry, not taken out if $p < 0.10$). Statistical analyses were conducted with PASW Statistics 18.0 software. A p value < 0.05 was considered statistically significant.

Results

Patient characteristics

402 out of 1283 study participants at the study site Göttingen were offered to participate in this substudy and 378 (94 %) agreed. Compared to the overall 1283 study participants, those included in this substudy were slightly younger (66.2 ± 7.0 vs. 67.3 ±8.1 years, $p < 0.001$), but gender, body mass index and weight were not significantly different. We excluded patients with predominately central apneas (n=14) and those with a known history of sleep apnea (n=12) from further analysis. Thus, 352 patients were included into the final analysis. Baseline characteristics of the three respiratory pattern groups are shown in Table 1. 21 patients had a severe OSA (AHI > 30 events/h). As a first finding, OSA was highly prevalent in this cardiovascular risk groups: 39 % (n=136) had no OSA, 40 % (n=140) had mild, and 22 % (n=76) had moderate/severe OSA.

Patients with OSA were older, less often females, more obese, and tended to have higher systolic blood pressure values and more heart failure than those without OSA. Pulmonary function did not differ between groups.

Polygraphy

Standard physical and clinical parameters obtained during polysomnography are depicted in Table 2. The median (25-75% percentile) recording time was 461 min (415 min - 510 min) and did not differ between groups. Desaturation index, minimal O_2 saturation and Epworth sleepiness scale index gradually worsened with increasing AHI frequency.

Echocardiographic parameters

Table 3 summarises echocardiographic parameters of cardiac function and remodelling. Systolic function was normal (mean ejection fraction 59 ± 10 %) and did not differ between groups. However, adverse LV remodelling was more pronounced in OSA patients: Left ventricular end-diastolic diameter was slightly larger in moderate/severe OSA, left ventricular

volumes tended to be higher and all parameters of LV hypertrophy gradually increased with increasing frequency of AHI. Traditional parameters of diastolic function showed no association with OSA, but tissue Doppler-derived indices of diastolic dysfunction showed significant differences: e´ was reduced in OSA, whereas E/e´ as a central parameter of diastolic dysfunction and estimate of left ventricular enddiastolic pressure significantly increased with increasing severity of OSA.

The presence of diastolic dysfunction was significantly associated with OSA. While 45 % of classical risk patients for abnormal diastolic function with an AHI < 5 had echocardiographic evidence of diastolic dysfunction, this number increased to 57 % in mild, and 70 % in moderate/severe OSA patients with a comparable cardiovascular risk factor background ($p=0.004$ for comparison of degrees of diastolic dysfunction with degrees of sleep apnea, $p=0.002$ for comparison of presence of diastolic dysfunction with presence of sleep apnea). Moreover, diastolic dysfunction was more severe with OSA as evidenced by an increase in participants with elevated filling pressure (Figure 1). Left atrial volume as a continuous marker of left atrial size significantly correlated with AHI ($r=0.259$, $p=0.002$, see figure 2). Left atrial volume to a lesser extent also correlated with BMI ($r=0.225$, $p<0.001$) and age ($r=0.141$, $p=0.008$).

To further substantiate the notion that OSA is associated with diastolic dysfunction, univariate and multivariate regression analyses were performed.

In univariate analysis, age, AHI, desaturation index, heart rate, body mass index, therapy with AT1 antagonists and left ventricular mass were associated with diastolic dysfunction (Table 4). These six variables as well as hypertension and diabetes were tested in a multivariate model. Only age, BMI, AHI and heart rate were independently associated with diastolic dysfunction and entered into the final model (Table 5). If patients with systolic dysfunction (EF < 50 %) and/or heart failure were excluded, the results remained similar apart from the fact that BMI was no longer significant ($p=0.099$).

Discussion

In this large cross-sectional cohort of patients with risk factors for diastolic dysfunction, moderate/severe obstructive sleep apnea was independently associated with impaired left ventricular filling. In our cohort, 21.6 % of the subjects had an AHI ≥ 15/h, which is higher than in the general population[9], but comparable to populations with heart failure[24], arterial hypertension[28] or coronary artery disease[10] as reported previously. Our data confirm the established impact of heart rate, body mass index and left ventricular mass on diastolic function. We found a high prevalence of diastolic dysfunction which probably is explained by the inclusion criteria of our study (age > 50 years, at least one risk factor for diastolic dysfunction etc.). We did not find an association between diabetes and diastolic function[29] which may be explained by the relative small number of patients included with a pre-diagnosed diabetes (n=55).

Obstructive sleep apnea and diastolic dysfunction

Our finding of an association of OSA with diastolic dysfunction is supported by other studies[18,20,21,22,30], although these studies are limited by a small sample size between 20 and 68 participants. In a cohort of more than 500 patients, Niroumand et al.[23] did not show an association of OSA with diastolic function. In this study, however, no tissue Doppler data were available and the diagnosis of diastolic dysfunction relied on the E/A ratio only. As the E/A ratio is decreased in stage 1 diastolic dysfunction (impaired relaxation), but pseudonormal in stage 2 diastolic dysfunction, a diagnosis of diastolic dysfunction based on E/A ratio only is not possible and discouraged by current guidelines. Rather, tissue Doppler is now regarded to be essential for the non-invasive diagnosis and grading of diastolic function[4]. Indeed, it has consistently been shown that the degree of diastolic dysfunction as classified by tissue Doppler is a strong predictor of mortality[31]. Due to this classification problem based on still limited knowledge on assessment of diastolic function at the time of their analysis, Niroumand et al.[23] may have missed a substantial subset of patients with diastolic dysfunction in their analysis.

In our cohort we found an odds ratio of about 2.0 for the presence of diastolic dysfunction in moderate to severe sleep apnea. This is comparable to the risk association of sleep apnea and arterial hypertension, heart failure and coronary artery disease in previous cross-sectional studies yielding multivariate odds ratios around 2[9,10,32,33,3435]. At present, the mechanisms explaining the relationship between HFprEF and OSA are not well defined. However, negative effects of sleep apnea on left ventricular structure and function independent of blood

pressure are well described. These effects might be related to the autonomic nervous system, clock genes, endothelial dysfunction, inflammation, blood sugar control or oxidative stress[8,9,11]. Recently it has been shown that treating OSA not only contributes to an improvement of systolic and diastolic blood pressure, but also effects on lipid levels, glycated hemoglobin levels, body mass index and abdominal fat content, established risk factors for HFprEF[4,36].

Central sleep apnea was rare in our cohort (< 4 %), which may be explained by the low prevalence of heart failure with reduced ejection fraction, where central apnea is much more common[37,38]. Nevertheless, recent data also showed a higher prevalence of OSA than CSA in heart failure with reduced ejection fraction[24]. Our results are in agreement with Bitter et al. [39], who reported a higher prevalence of OSA (40%) than CSA (30%) in patients suffering from symptomatic HFprEF. Furthermore Chan et al. demonstrated in a small study of symptomatic HFprEF a prevalence of sleep disordered breathing of 55 %, with a majority of these patients suffering from OSA[40]. However, in both studies CSA was seen more often than in our study, possibly because our patients were at an earlier stage of cardiac disease. This may be explained by the fact that most of our patients had only diastolic dysfunction, not symptomatic HFprEF as in the above mentioned papers[39,40]. Our results of an independent association of OSA with diastolic dysfunction support the concept of treating OSA to improve diastolic function and to prevent symptomatic HFprEF. Several small studies so far indeed could demonstrate positive effects of continuous positive airway pressure treatment of OSA on diastolic function[15,19,41].

Limitations

We evaluated sleep apnea by ambulatory polygraphy, not polysomnography. However, different studies investigating the ability of polygraphy to detect sleep disordered breathing showed a high diagnostic accuracy of the portable recording devices[42,43,44]. It is unlikely, that the additional information on sleep stages given by polysomnography would profoundly modify the results.

The definition and grading of diastolic dysfunction is still a matter of debate and indeed, various different classifications have been used. We can not rule out that in other classifications of diastolic dysfunction, the results would have been different. We chose to use the recent classification by Nagueh et al.[27], although classification of cases is often not unequivocally. We retested the hypothesis with another recently published classification[6] and

found similar results of an independent association of moderate/severe OSA with diastolic dysfunction. In addition, we also analysed well validated continuous quantitative parameters of diastolic function (e. g. e´, E/e´) that are independent from any classification system for the degree of diastolic dysfunction and these parameters were also negatively affected by sleep apnea in our study. Summarizing this data, we think there is robust evidence to support our findings.

A minority of included patients had heart failure and/or systolic dysfunction. Our results (especially the multivariate analysis) remained unchanged if these patients were excluded. However, the number of patients with heart failure and/or systolic dysfunction was too small to investigate whether the impact of OSA in this subgroup is similar to patients with preserved ejection fraction and without heart failure.

Finally, multivariate analysis can only describe an association, but does not prove cause and effect. However, the results from our large cross sectional primary care cohort are corroborated by the findings from small but well controlled randomized trials using CPAP in OSA patients without hypertension or cardiovascular disease[12,13]. Furthermore, blood pressure independent negative effects of OSA on the left ventricle are well described as detailed above.

Summary

In a large primary care cohort of patients with risk factors for diastolic dysfunction, the presence of moderate/severe OSA is independently associated with the prevalence and severity of diastolic dysfunction. This cross sectional data support small, well controlled trials in patients without cardiovascular risk factors showing an improvement of diastolic function with CPAP. Thus it might be inferred that OSA is a promising target for improving diastolic function and consecutively reduce the burden of HFprEF.

Acknowledgement

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Tables

Table 1: Demographics of the study participants, according to sleep apnea severity.

Table 2: Respiratory data according to sleep apnea severity. The desaturation index was based on oxygen desaturations ≥ 3 %.

Table 3: Results according to sleep apnea severity.

Table 4: Univariate regression analysis to identify predictors for diastolic dysfunction.

Table 5: Multivariate regression analysis to identify predictors for diastolic dysfunction.

Figure Legends

Figure 1: Prevalence of diastolic dysfunction according to sleep apnea severity. P value for the comparison of degrees of diastolic dysfunction to degrees of sleep apnea (Chi-square-Test).

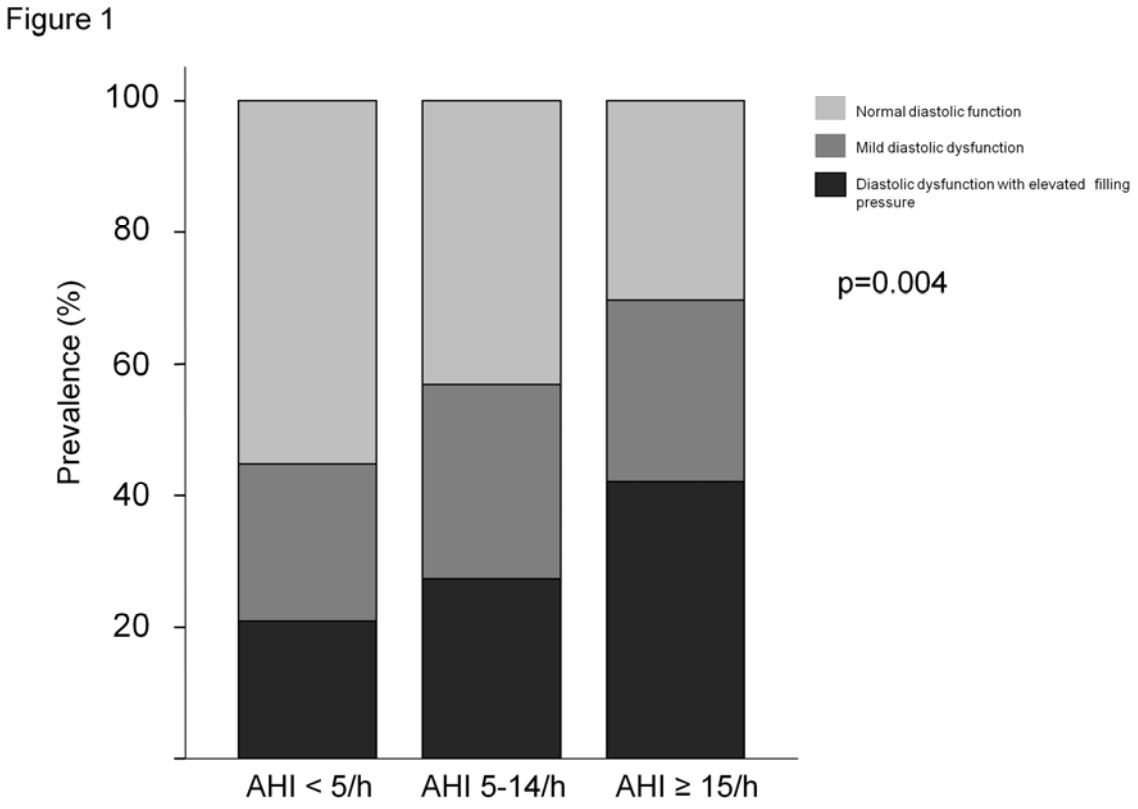

Figure 2: Bivariate correlation analysis for Apnea/Hypopnea-index and left atrial volume.

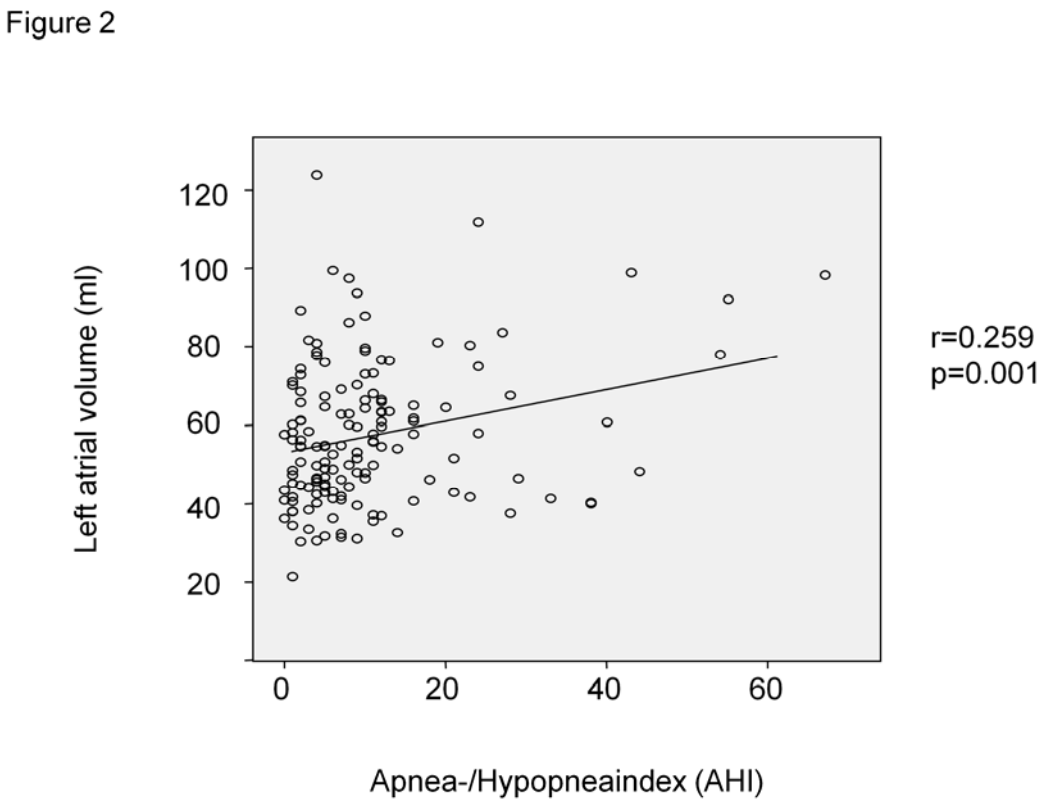

Table 1

	AHI < 5/h (n=136)	AHI 5-14/h (n=140)	AHI ≥ 15/h (n=76)	P
Demographics				
Age (yrs)	64 ± 7	67 ± 6*	68 ± 8*	0.001
Female (%)	57.4	54.3	36.8	0.012
Body mass index (kg/m^2)	28.1 ± 4.6	28.6 ± 4.0	30.1 ± 5.0*	0.011
Systolic blood pressure (mmHg)	149 ± 20	154 ± 21	152 ± 18	0.121
Diastolic blood pressure (mmHg)	83 ± 12	85 ± 12	85 ± 11	0.133
Heart rate (bpm)	71 ± 12	71 ± 12	69 ± 13	0.499
Atrial fibrillation (%)	1.5	0.7	1.3	0.759
Hypertension (%)	87.5	85.0	93.4	0.195
Diabetes (%)	14.7	16.4	14.5	0.899
Hyperlipidemia (%)	41.9	34.3	47.4	0.147
Coronary artery disease (%)	18.4	12.9	17.1	0.432
Heart failure (%)	5.1	5.7	11.8	0.143
Current smoker (%)	10.3	7.9	6.6	0.155
Previous smoker (%)	36.0	30.9	47.4	0.155
Pack years	20 ± 17	21 ± 21	24 ± 25	0.642
Bodyplethysmography				
FEV 1 (% predicted)	92 ± 17	93 ± 18	92 ± 14	0.752
Vital capacity (% predicted)	88 ± 14	90 ± 16	88 ± 14	0.530
Residual volume (% predicted)	106 ± 33	109 ± 30	104 ± 27	0.518
Total lung capacity (% predicted)	93 ± 14	95 ± 13	92 ± 14	0.284
Total airway resistance (kPa*l^{-1}*s)	0.36 ± 0.19	0.34 ± 0.14	0.33 ± 0.15	0.394
Medication				
ACE-inhibition (%)	41.9	45.7	44.7	0.809
AT1-antagonist (%)	10.3	11.4	31.6	<0.001
Beta-blockers (%)	41.9	45.7	55.3	0.171
Calcium channel blockers (%)	19.9	13.6	32.9	0.003
Diuretics (%)	44.1	48.6	61.8	0.044
Statins (%)	26.5	21.4	31.6	0.251

* $p < 0.05$ vs. AHI < 5/h

Table 2

	AHI < 5/h (n=136)	**AHI 5-14/h (n=140)**	**AHI ≥ 15/h (n=76)**	**p**
Recording time (minutes)	463 (413-510)	463 (421-512)	454 (410-501)	0.874
Average O_2-saturation (%)	95 (93 – 95)	94 (93 – 95)	94 (93 – 95)	0.003
Desaturation index (%)	5 (2 – 9)	12 (7 – 17)	20 (15 – 34)	< 0.001
Minimal O_2-saturation (%)	82 (76 – 87)	81 (74 – 85)	79 (73 – 83)	0.037
Mean heart rate (bpm)	60 ± 14	61 ± 9	60 ± 11	0.889
Epworth Sleepiness Scale	5 (3 – 8)	5 (4 – 8)	7 (4 – 9)	0.184

Table 3

	AHI < 5/h (n=136)	**AHI 5-14/h (n=140)**	**AHI ≥ 15/h (n=76)**	**p**
NT-proBNP (pg/ml)	84 (45-184)	102 (57-191)	135 (69-261)	0.062
6- minute walking distance (m)	560 ± 81	551 ± 84	535 ± 87	0.134
Echocardiography				
Ejection fraction (%)	59 ± 8	60 ± 11	58 ± 9	0.268
Ejection fraction < 50 % (%)	8.8	6.4	13.2	0.249
IVS (mm)	11.7 ± 1.6	12.2 ± 1.9*	12.4 ±1.8*	0.006
LVPW (mm)	10.8 ± 1.4	11.2 ± 1.4*	11.3 ± 1.4*	0.006
Left ventricular mass (g)	220 ± 65	230 ± 58	254 ± 76*$	0.001
Left ventricular mass index (g/m^2)	113 ± 26	119 ± 26	125 ± 29	0.012
LVEDD (mm)	50 ± 6	50 ± 5	52 ± 7*$	0.015
Left ventricular endsystolic volume (ml)	41 ± 20	39 ± 15	45 ±27	0.166
Left ventricular endsystolic volume index (ml/m^2)	21 ± 9	20 ± 7	22 ± 11	0.366
Left ventricular enddiastolic volume (ml)	95 ± 31	91 ±25	99 ± 32	0.257
Left ventricular enddiastolic volume index (ml/m^2)	49 ± 13	47 ± 11	49 ± 14	0.635
Left atrial volume (ml)	48 ± 19	50 ± 16	57 ± 21	0.110
Left atrial volume index (ml/m^2)	24 ± 8	26 ± 8	28 ± 8	0.254
E/A ratio	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.4	0.418
EDCT (ms)	240 ± 69	257 ± 76	253 ± 70	0.153
IVRT (ms)	98 ± 17	100 ± 19	96 ± 19	0.291
e´ (medial)	5.9 ± 1.7	5.6 ± 1.5	5.6 ± 1.6	0.151
e´ (lateral)	8.3 ± 2.6	7.8 ± 2.2	7.4 ± 2.1*	0.021
E/e´ (mean) ratio	11.0 ± 3.6	11.7 ± 3.5	12.7 ± 5.3*	0.011

* $p < 0.05$ vs. AHI < 5/h

$ $p < 0.05$ vs. AHI 5-14/h

IVS: Interventricular septum. LVPW: Left ventricular posterior wall. LVEDD: Left ventricular enddiastolic diameter. E/A ratio: Ratio of Early (E) to late (A) pulsed wave Doppler of diastolic ventricular fillig. EDCT: E wave deceleration time. IVRT: Isovolumetric relaxation time. e´: Tissue Doppler of early diastolic ventricular filling. E/e´: Ratio of early diastolic pulsed wave Doppler to early diastolic Tissue Doppler (mean of medial and lateral mitral annulus).

Table 4

Variable	p (univariate analysis)	Odd´s ratio	R^2
Age (per year)	< 0.001	1.136 (1.093 - 1.180)	0.193
Female sex	0.663	0.910 (0.597 - 1.389)	0.001
Sleep apnea (AHI ≥ 15/h)	0.004	2.221 (1.290 - 3.827)	0.033
AHI (Events per hour)	0.001	1.041 (1.017 – 1.065)	0.052
Desaturation index (%)	0.003	1.031 (1.011 – 1.052)	0.003
Hypertension	0.487	1.257 (0.659 - 2.397)	0.002
Diabetes	0.149	1.563 (0.853 - 2.865)	0.008
CAD	0.092	1.676 (0.919 - 3.058)	0.011
Left ventricular mass (per g)	0.021	1.004 (1.001 - 1.007)	0.021
Left ventricular enddiastolic diameter	0.442	1.015 (0.977 - 1.054)	0.002
Body mass index (per kg/m2)	0.005	1.075 (1.022 - 1.130)	0.032
Heart rate (per bpm)	0.010	1.024 (1.006 - 1.042)	0.026
Systolic blood pressure (per mmHg)	0.196	1.007 (0.996 - 1.018)	0.006
Diastolic blood pressure (per mmHg)	0.391	0.992 (0.974 - 1.010)	0.003
AT1 antagonists	0.032	1.966 (1.060 - 3.647)	0.018
Calcium channel blockers	0.718	0.925 (0.606 - 1.412)	0.000
Diuretics	0.044	1.547 (1.012 - 2.365)	0.016
Loop diuretcs	0.181	1.809 (0.759 - 4.311)	0.007
Thiazide	0.063	1.501 (0.979 - 2.300)	0.013
Other diuretics	0.233	1.828 (0.678 - 4.925)	0.006
Number of antihypertensives	0.080	1.161 (0.982 – 1.372)	0.012

R^2 is Nagelkerkes R^2.

Table 5

	Odds ratio (95 % CI)	**p**
Age (per year)	1.136 (1.090 – 1.185)	< 0.001
AHI (per event/h)	1.038 (1.010 – 1.067)	0.008
Body mass index (per kg/m^2)	1.073 (1.012 – 1.138)	0.018
Heart rate (per bpm)	1.038 (1.017 – 1.059)	< 0.001

R^2 = 0.275. R^2 is Nagelkerkes R^2.

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