Archives of Cardiovascular Disease (2015) 108, 480—490

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

CLINICAL RESEARCH

Left ventricular diastolic dysfunction in obstructive sleep apnoea syndrome by an echocardiographic standardized approach: An observational study

Syndrome d'apnée du sommeil obstructif et dysfonction diastolique ventriculaire gauche par approche standardisée : une étude observationnelle

Diane Bodez[a], Sylvie Lang[a], Catherine Meuleman[a], Louise Boyer-Châtenet[a], Xuan-Lan Nguyen[b], Laurie Soulat-Dufour[a], Franck Boccara[a], Bernard Fleury[b], Ariel Cohen[a,*]

[a] *Service de cardiologie, hôpital Saint-Antoine, Assistance publique—Hôpitaux de Paris, université Pierre-et-Marie-Curie, 184, rue du faubourg Saint-Antoine, 75571 Paris cedex 12, France*

[b] *Centre d'évaluation et traitements des troubles du sommeil, hôpital Saint-Antoine, Assistance publique—Hôpitaux de Paris, 184, rue du faubourg Saint-Antoine, 75571 Paris cedex 12, France*

Received 27 January 2015; received in revised form 9 March 2015; accepted 18 March 2015
Available online 8 June 2015

KEYWORDS
Obstructive sleep apnoea syndrome;

Summary
Background. — The association between obstructive sleep apnoea syndrome (OSAS), left ventricular (LV) diastolic dysfunction and LV geometry remains controversial because of coexisting disorders.

Abbreviations: A, late diastolic mitral peak flow velocity; AASM, American Academy of Sleep Medicine; ABPM, ambulatory blood pressure monitoring; AH, apnoea-hypopnoea; AHI, apnoea-hypopnoea index; BMI, body mass index; BSA, body surface area; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; E, early diastolic mitral peak flow velocity; e′, early diastolic mitral annular velocity; ECG, electrocardiogram; LAA, left atrial area; LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMi, left ventricular mass index; OSAS, obstructive sleep apnoea syndrome; PHT, pulmonary hypertension; RWT, relative wall thickness; SDB, systolic blood pressure; sPAP, systolic pulmonary arterial pressure; TDI, tissue Doppler imaging.

* Corresponding author. Service de cardiologie, hôpital Saint-Antoine, Assistance publique—Hôpitaux de Paris, université Pierre-et-Marie-Curie, 184, rue du Faubourg-Saint-Antoine, 75571 Paris cedex 12, France.
E-mail address: ariel.cohen@aphp.fr (A. Cohen).

http://dx.doi.org/10.1016/j.acvd.2015.03.006

Left ventricular geometry;
Left ventricular diastolic function

Aims. — To evaluate LV diastolic dysfunction and its independent predictors in a real-life cohort of OSAS patients, by a standardized approach.
Methods. — We consecutively included 188 OSAS patients after an overnight polysomnography to undergo clinical evaluation, ambulatory blood pressure measurement and complete echocardiography, combining M-mode, two-dimensional Doppler and tissue Doppler imaging modes. Correlations between OSAS severity and clinical and echocardiographical variables were assessed, and logistic regression models were used to identify possible determining factors of LV diastolic dysfunction.
Results. — Most patients were hypertensive ($n = 148$, 78.7%) and already receiving treatment by continuous positive airway pressure ($n = 158$, 84.5%). The prevalence of LV hypertrophy, defined by LV mass index (LVMi) normalized by height$^{2.7}$, was 12.4%, with a significant correlation with hypertension ($P = 0.004$). The apnoea-hypopnoea index was correlated with body mass index ($P < 0.0001$), 24-hour systolic blood pressure ($P = 0.01$) and LVMi normalized by height$^{2.7}$ ($P = 0.03$). Diastolic function assessed by a global approach was impaired for 70 patients (37.2%) and none of the OSAS severity variables was a determining factor after multivariable analysis with adjustment for age and sex.
Conclusion. — Diastolic dysfunction assessed by a standardized approach is common in OSAS and should be routinely evaluated; it is independently predicted by none of the respiratory severity variables.

MOTS CLÉS
Syndrome d'apnée du sommeil obstructif ;
Géométrie ventriculaire gauche ;
Fonction diastolique ventriculaire gauche

Résumé
Contexte. — L'association entre le syndrome d'apnée du sommeil obstructif (SASO), la dysfonction diastolique ventriculaire gauche (VG) et la géométrie VG reste controversée en raison de nombreux facteurs prédisposants partagés.
Objectifs. — Évaluer la fonction diastolique VG et ses déterminants dans une cohorte de patients SASO tout-venant, par une approche standardisée.
Méthodes. — Après polysomnographie, 188 patients consécutifs ont eu un bilan cardiovasculaire avec évaluation clinique, mesure ambulatoire de la pression artérielle, et échocardiographie avec modes TM, 2D, doppler, et doppler tissulaire. Les corrélations entre sévérité du SASO et les paramètres cliniques et échographiques ont été analysées. Les potentiels déterminants de la dysfonction diastolique VG ont été étudiés par régression logistique.
Résultats. — La plupart des patients étaient hypertendus ($n = 148$, 78,7 %) et étaient déjà traités par ventilation en pression positive continue ($n = 158$, 84,5 %). La prévalence de l'hypertrophie VG établie sur la masse VG indexée à la taille^{2,7} (MVGi) était de 12,4 % avec une corrélation significative avec l'hypertension ($p = 0{,}004$). L'index apnée-hypopnée était corrélé à l'indice de masse corporelle ($p < 0{,}0001$), la pression systolique des 24 h ($p = 0{,}01$) et la MVGi ($p = 0{,}03$). La fonction diastolique étudiée par approche standardisée était anormale pour 70 (37,2 %) patients. Aucun des paramètres de sévérité du SASO n'était prédicteur indépendant de dysfonction diastolique après analyse multivariée ajustée sur l'âge et le sexe.
Conclusion. — La dysfonction diastolique est fréquente chez les patients SASO et doit être recherchée en routine. Elle n'est prédite de façon indépendante par aucun des paramètres de sévérité respiratoires.

Background

Obstructive sleep apnoea syndrome (OSAS) is a common chronic respiratory sleep disorder characterized by periodic reduction or cessation of breathing due to narrowing of the upper airways during sleep; it occurs in 2% of middle-aged women and 4% of men [1]. OSAS is a well-established risk factor for several cardiovascular complications, including heart failure [2], acute myocardial infarction [3], arrhythmias [4], hypertension [5], pulmonary hypertension [6] and stroke [7]. The pathophysiological effects of obstructive apnoea on the cardiovascular system involve several mechanical, haemodynamic, neurohumoral, inflammatory, endothelial and oxidative mechanisms [8].

In addition, left ventricular hypertrophy (LVH), which is associated with left ventricular (LV) diastolic dysfunction

[9], is often observed in OSAS patients. LV diastolic dysfunction is also known to be an independent risk factor for cardiovascular morbidity and mortality [10], like LVH and concentric remodelling [11]. Whereas the association between OSAS and some cardiovascular complications is clear, the association between OSAS on the one hand and LVH or LV diastolic dysfunction on the other, still remains controversial [12—15], because of several coexisting disorders that lead to LVH and LV diastolic dysfunction, such as obesity [16], hypertension [17] and diabetes mellitus [18]. Moreover, to our knowledge, previous studies that investigated the relationship between OSAS and LV diastolic dysfunction all used separated criteria, with no global approach.

The aim of this study was to evaluate the prevalence of LV diastolic dysfunction and to identify its determining factors, in a real-life large cohort of OSAS patients, by an echocardiographic multivariable approach using two-dimensional mode Doppler, conventional Doppler and tissue Doppler imaging (TDI).

Methods

Population

We conducted an observational cohort study in 188 patients with OSAS who were referred consecutively by Saint-Antoine's Sleep Laboratory (Paris, France) for cardiovascular evaluation between March 2005 and January 2010. There were no exclusion criteria. After sleep study in Saint-Antoine's expertise centre, each patient underwent a clinical evaluation during a consultation, an electrocardiogram (ECG), 24-hour ambulatory blood pressure monitoring (ABPM), biological tests and transthoracic echocardiography. Demographic characteristics, measure of daytime sleepiness by the Epworth sleepiness scale and cardiovascular risk factors (including hypertension, diabetes mellitus, hyperlipidaemia, current or former smoking, coronary heredity and obesity) were reported. Hypertension was defined as the use of antihypertensive medication and/or systolic blood pressure (SBP) $\geq$140 mmHg and/or diastolic blood pressure (DBP) $\geq$90 mmHg during consultation and/or blood pressure $\geq$125/80 mmHg during ABPM [19]. A dipper pattern was defined by a nocturnal fall in blood pressure $\geq$10%. Nocturnal hypertension was defined as nocturnal blood pressure $\geq$120/70 mmHg; diurnal hypertension was defined as diurnal blood pressure $\geq$130/85 mmHg. Masked hypertension was considered to be present when normal blood pressure during consultation was associated with hypertension on ABPM. Obesity was defined as a body mass index (BMI) $\geq$30 kg/m^2; metabolic syndrome was defined according to the National Cholesterol Education Program — Adult Treatment Panel III guidelines [20]. According to the Declaration of Helsinki, all information about participation in non-interventional clinical studies was given to the patients.

Sleep study

All participants were referred after an attended overnight polysomnography using the Cidelec® system (Angers, France), which confirmed the diagnosis of OSAS according to the recommendations of the American Academy of Sleep Medicine (AASM) [21]. The following channels were used: two-channel electroencephalogram, electromyogram, ECG, electro-oculogram, body position, chest and abdominal excursions, airflow (with an oronasal transducer) and arterial oxygen saturation by finger pulse oximetry. Apnoea was defined as a complete cessation of airflow at the nose and mouth for at least 10 seconds, and was classified as obstructive, central or mixed, according to the presence or absence of respiratory efforts. Hypopnoea was defined as a partial closure, resulting in a diminution of airflow to <50% of baseline for at least 10 seconds or <70% associated with a microarousal or oxygen desaturation of >3%. The apnoea-hypopnoea index (AHI) was defined as the number of apnoeas and hypopnoeas per hour of sleep. According to the AASM, the severity of OSAS was classified as mild ($5 \leq$ AHI < 15 events/hour), moderate ($15 \leq$ AHI ≤ 30 events/hour) and severe (AHI >30 events/hour). Desaturation time was defined as the percentage of sleep time with oxygen saturation <90%.

Echocardiography

Transthoracic echocardiography was performed with Vingmed Vivid 7 (GE Healthcare, Horton, Norway) and iE33 (Philips Healthcare, Bothell, WA, USA) ultrasound machines, with a 2.5 MHz probe. LV dimensions and wall thickness were measured according to American Society of Echocardiography recommendations [22], from the parasternal long-axis view using M-mode measurements. Left ventricular mass (LVM) was calculated by the formula described by de Simone et al. [23] and was normalized by body surface area (BSA) and height$^{2.7}$. According to the European recommendations [24], LVH was defined as an LVM index (LVMi) >115 g/m^2 for men and >95 g/m^2 for women or >50 g/m$^{2.7}$ for both; LVH was defined as concentric if relative wall thickness (RWT) was >0.42 and as eccentric if RWT was $\leq$0.42. Concentric remodelling was defined as a normal LVM associated with an RWT >0.42. LV systolic function was evaluated by LV ejection fraction (LVEF) by the biplane Simpson method from the apical four-chamber and two-chamber views; it was considered abnormal if <50%. To evaluate LV diastolic function, transmitral pulsed-wave Doppler velocities and pulmonary venous flow were recorded from the apical four-chamber view, with a 2 mm Doppler sample placed, respectively, between the tips of the mitral leaflets and in one upper pulmonary vein (usually the right); pulsed-wave TDI was recorded at the lateral mitral annulus from the apical four-chamber view, using pulsed-wave spectral Doppler. Early diastolic mitral annular velocity (e′) was measured and the early diastolic mitral peak flow velocity/e′ ratio (E/e′) was calculated. Left atrial area (LAA) and volume (LAV) were evaluated from the apical four-chamber and two-chamber views. LV diastolic function was assessed by a multivariable approach, adapted from the American Society of Echocardiography recommendations, based on lateral e′, LAA, E/A ratio (where A is late diastolic mitral peak flow velocity), E-wave deceleration time, E/e′ ratio and pulmonary venous flow [25]. Systolic (sPAP) and mean (mPAP) pulmonary arterial pressure were calculated using the modified Bernoulli equation and conventional Doppler from the physiological tricuspid and pulmonary regurgitations, respectively [26,27]. Patients with sPAP $\geq$45 mmHg

and/or mean pulmonary arterial pressure ≥25 mmHg were considered to have pulmonary hypertension (PHT). All echocardiograms were performed by an experienced echocardiographer. All measurements were performed off-line using custom software (Echopac; GE Healthcare), in three cardiac cycles, by the same investigator, who was blinded to the patient's data.

Statistical analyses

Data are presented as medians with interquartile ranges. Comparisons between patients with or without LVH in relation to arterial hypertension, diabetes and BMI were made using the χ^2 test or Fisher's exact test. Spearman's correlation analysis was used to assess the possible relationship between severity of OSAS and clinical or echocardiographic variables. To identify determining factors of LV diastolic dysfunction, logistic regression models were used. For each continuous variable, the choice between continuous, categorical or transformed classification was based on the lowest value of Akaike's information criterion for the corresponding univariate logistic regression model. To avoid the colinearity problem in the models, the different variables linked to a given entity were grouped together in a family (e.g. hypertension and 24-hour SBP), as recommended [28]; then, each variable in a given family was entered in a stepwise multivariable model, and variables with *P*-values <0.10 were retained. Finally, a multivariable model adjusted for all selected variables was constructed. A *P*-value <0.05 was considered to be statistically significant for all analyses. All statistical analyses were performed using STATA® software, version 12 (StataCorp LP, College Station, TX, USA).

Results

Clinical characteristics

Between March 2005 and January 2010, 188 consecutive patients were included. Baseline clinical characteristics are shown in Table 1. Most patients ($n = 157$, 83.5%) were men; the median age was 51.5 (46.0—57.0) years. One hundred and forty-eight (78.7%) patients were objectively hypertensive, whereas 70 of them (47.2%) reported known hypertension. Half of the hypertensive patients presented a non-dipper profile on data from ABPM. As an inclusion criterion, all patients had OSAS; 165 (87.8%) were already treated for OSAS, mostly with continuous positive airway pressure (CPAP; $n = 158$, 84.5%). The median AHI was 48.4 (32.0—71.0) events/hour and most patients had severe OSAS, with AHI >30 events/hour ($n = 159$, 84.6%). All of them presented a sinus rhythm.

Table 1 Baseline clinical characteristics.

Characteristic	OSAS patients ($n = 188$)
Men	157 (83.5)
Age (years)	51.5 (46.0—57.0)
Hypertension	148 (78.7)
Known hypertension	70 (47.2)
Masked hypertension	44 (23.4)
Nocturnal hypertension ($n = 185$)	112 (60.5)[a]
Diurnal hypertension	120 (63.8)
Non-dipper ($n = 185$)	90 (48.7)[a]
Diabetes	23 (12.5)
Metabolic syndrome	80 (42.6)
Current smoker	48 (25.5)
Obesity	105 (55.9)
BMI (kg/m²)	31.5 (27.3—35.2)
Fasting glycaemia (mmol/L; n = 183)	5.3 (4.9—5.7)[a]
Triglycerides (g/L; n = 184)	1.21 (0.96—1.78)[a]
Creatinine (μmol/L; n = 185)	94 (86—103)[a]
OSAS treatment, yes	165 (87.8)
Treatment with CPAP ($n = 187$)	158 (84.5)
AHI (events/hour)	48.4 (32.0—71.0)
Desaturation time (%; n = 180)	8 (2.0—25.5)[a]
Epworth sleepiness score (n = 178)	11 (7—15)
24-hour heart rate (bpm)	74 (68—82)
24-hour SBP (mmHg)	130 (122—140)
24-hour DBP (mmHg)	78 (74—84)

Data are expressed as number (%) or median (interquartile range). AHI: apnoea-hypopnoea index; BMI: body mass index; bpm: beats per minute; CPAP: continuous positive airway pressure; DBP: diastolic blood pressure; OSAS: obstructive sleep apnoea syndrome; SBP: systolic blood pressure.
[a] Only available for patients without missing data.

Left ventricular geometry

Echocardiographic characteristics are shown in Table 2. Nineteen (10.1%) patients had inadequate two-dimensional images for assessment of LV mass and geometry. Among the 169 remaining patients, the prevalence of LVH was different according to the corrective factor used (BSA or height$^{2.7}$): 6.5% if LVMi normalized by BSA; 12.4% if normalized by height$^{2.7}$. In the latter case, LVH was mostly eccentric ($n = 14$ eccentric versus $n = 7$ concentric). LV geometry was normal for 136 (80.5%) patients with LVMi corrected by BSA, and for 127 (75.2%) patients with LVMi corrected by height$^{2.7}$. There was a significant correlation between hypertension and LV geometry, but only if assessed by LVMi normalized

Table 2 Baseline echocardiographic characteristics.

Characteristic	OSAS patients ($n = 188$)
LVEF <50%	3 (1.6)
LVH (BSA; n = 169)	11 (6.5)[a]
LVH (height$^{2.7}$; n = 169)	21 (12.4)[a]
LVMi (n = 169)	
Normalized by BSA	76.9 (67.7—88.1)[a]
Normalized by height$^{2.7}$	35.9 (30.3—43.7)[a]
LVEDD (mm; n = 185)	51.3 (48.0—54.7)[a]
LVESD (mm; n = 186)	33.0 (29.2—36.8)[a]
RWT (n = 169)	0.35 (0.31—0.39)[a]
LV geometry (BSA; n = 169)	
Normal	136 (80.5)[a]
Concentric remodelling	22 (13.0)[a]
Concentric hypertrophy	6 (3.6)[a]
Eccentric hypertrophy	5 (3.0)[a]
LV geometry (height$^{2.7}$; n = 169)	
Normal	127 (75.2)[a]
Concentric remodelling	21 (12.4)[a]
Concentric LVH	7 (4.1)[a]
Eccentric LVH	14 (8.3)[a]
LAA (cm^2; n = 168)	17.9 (15.3—20.8)[a]
LAV (mL/m^2; n = 94)	22.9 (18.8—29.2)[a]
Pulmonary hypertension (n = 178)	11 (5.9)[a,b]
Diastolic function variables	
Lateral e′ velocity ($n = 169$)	0.11 (0.09—0.12)[a]
E/A ratio	1.06 (0.88—1.23)
E-wave deceleration time ($n = 172$)	184.3 (164.8—204.5)[a]
E/e′ ratio ($n = 169$)	7.0 (5.7—8.3)[a]
pA-mA duration ($n = 156$)	−33.5 (−46.5—−17.3)[a]
Diastolic function by a standardized approach	
Normal diastolic function	118 (62.8)
Abnormal diastolic function	70 (37.2)

Data are expressed as number (%) or median (interquartile range). BSA: body surface area; E/A: early/late diastolic mitral peak flow velocity ratio; E/e′: mitral early diastolic peak flow velocity/early diastolic velocity by TDI ratio; LAA: left atrial area; LAV: left atrial volume; LV: left ventricular; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end systolic diameter; LVH: left ventricular hypertrophy; LVMi: left ventricular mass index; mA: late diastolic mitral pulse-wave velocity duration; pA: late diastolic pulmonary pulse-wave velocity duration; RWT: relative wall thickness.

[a] Only available for patients without missing data.

[b] Pulmonary hypertension defined by systolic pulmonary arterial pressure ≥45 mmHg for seven patients, and by mean pulmonary arterial pressure ≥25 mmHg for four patients.

by height$^{2.7}$ ($P = 0.004$; Table 3). We did not observe a significant difference in LV geometry according to the type of hypertension (known, masked or absent) or according to its profile (dipper or non-dipper; data not shown).

Correlations between AHI and desaturation time on the one hand, and clinical and echocardiographic characteristics on the other hand, are shown in Supplementary data, Tables S1 and S2, respectively. AHI correlated significantly with BMI, triglycerides, desaturation time and 24-hour SBP because of night SBP (Supplementary data, Table S1). Concerning echocardiographic characteristics, AHI correlated significantly with LAA and LVMi only if normalized by height$^{2.7}$ (Supplementary data, Table S2). However, only BMI and desaturation time exhibited relevant correlation coefficients (0.36 and 0.56, respectively). About desaturation time, we did not observe any correlation with night SBP, but correlations with fasting glycaemia, LV diameters and LVMi (normalized by height$^{2.7}$) were statistically significant. All correlation coefficients were <0.5.

Left ventricular diastolic function

Regarding LV function, only three (1.6%) patients presented LV systolic dysfunction, which was moderate in two cases (LVEF ≥45%). By a standardized approach using a decisional tree, 70 patients presented abnormal diastolic function (37.2%; Fig. 1 and Table 2). Baseline characteristics of patients according to the diastolic function classification (normal diastolic function, diastolic dysfunction grade I, grade II, grade III) are shown in Table 4. Fig. 2 shows respiratory severity variables across the four groups. Among the 34 patients without hypertension, diabetes, severe obesity and LVH, five (17%) patients presented LV diastolic dysfunction.

Logistic regression analyses, using diastolic dysfunction assessed by a standardized approach as a dependent variable, are shown in Table 5. Two models are presented, according the corrective factor used for the LVMi (BSA or height$^{2.7}$). The univariate analysis showed that age, presence of hypertension and 24-hour SBP were predictors of diastolic dysfunction. The multivariable analyses, after adjustment for age and sex and stepwise regression, showed that severity variables of OSAS and LVMi, whatever the corrective factor used, were not independent predictors of diastolic dysfunction.

Discussion

This retrospective study reports the clinical and echocardiographic characteristics of a real-life large cohort of OSAS patients, focusing on diastolic function assessed by a standardized approach.

Left ventricular geometry

Our results show different rates of LVH depending on whether LVMi was normalized by BSA or height$^{2.7}$. Indeed, the prevalent LVH was twice as high if LVMi was corrected by height$^{2.7}$. These data are consistent with those reported by de Simone et al. [23], who found that LVH was underestimated in obese patients if assessed by LVMi normalized by BSA or body weight, and who recommend LVM indexation

Table 3 Left ventricular geometry according to the presence of hypertension.

	Hypertension ($n = 125$)	No hypertension ($n = 44$)	P
LV geometry (BSA)			0.09
Normal	99 (79.2)	37 (84.1)	
LVH	11 (8.8)	0	
Concentric remodelling	15 (12.0)	7 (15.9)	
LV geometry (height$^{2.7}$)			0.004
Normal	90 (72.0)	37 (84.1)	
LVH	21 (16.8)	0	
Concentric remodelling	14 (11.2)	7 (15.9)	

Data are expressed as number (percentage). BSA: body surface area; LV: left ventricular; LVH: left ventricular hypertrophy.

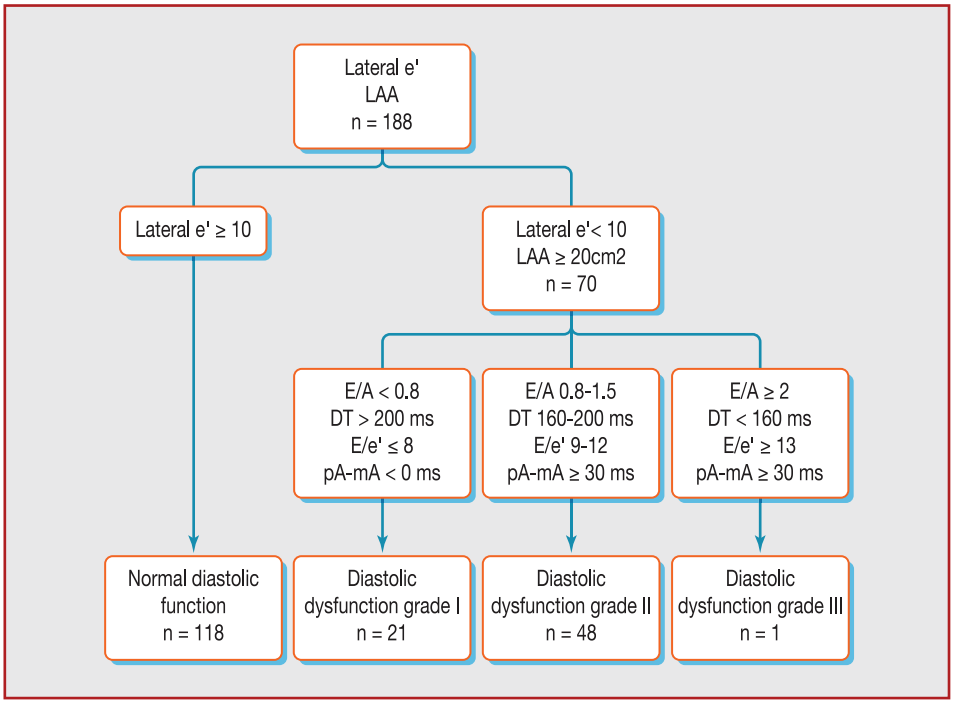

Figure 1. Decisional tree of diastolic function evaluation by standardized approach. DT: desaturation time; e′: early diastolic mitral annular velocity; E/A ratio: early diastolic mitral peak flow velocity/late diastolic mitral peak flow velocity; LAA: left atrial area; mA: late diastolic mitral pulse-wave velocity duration; pA: late diastolic pulmonary peak flow velocity.

method based on obesity-independent measure of body size. Indeed, more than half of our patient cohort were obese, as in most OSAS patient cohorts [5]. Given that LV geometry has a well-known prognostic value, and that LVH assessed by LVMi (height$^{2.7}$) is a stronger independent predictor of incident cardiovascular diseases than LVMi (BSA) [29], these results confirm that the use of LVMi corrected by height$^{2.7}$ is the appropriate method for assessment of LV geometry in OSAS patients. Furthermore, we observed a significant association between hypertension and LVMi normalized by height$^{2.7}$. Despite the high prevalence of hypertension in our cohort, we observed, like Baguet et al. [30], a lower rate of LVH than previously reported, with a large majority having normal LV geometry. Indeed, in a large cross-sectional analysis based on the Sleep Heart Health Study, Chami et al. [31] reported an LVH prevalence of up to 33% according to the severity of OSAS and the type of LVH; likewise, Noda et al. [32] reported an LVH prevalence of 41.2% in 51 mild-to-severe OSAS patients. Explanations for this discrepancy might be the young age and the low severity of hypertension in the present cohort, with a mean 24-hour SBP of 130 mmHg and a mean 24-hour DBP of 78 mmHg, whereas hypertension is a major confounding factor of LVH in OSAS populations [30,32]. However, Koga et al. [33] found only 5% with normal LV geometry in 37 OSAS men presenting the same clinical baseline characteristics as those in the present study. Yet, in the study by Koga et al., patients did not undergo ABPM; this might underestimate the prevalence of hypertension. Moreover, in a large cross-sectional study, Niroumand et al. [15] found that OSAS does not increase LVM independently of obesity, hypertension or advanced age. That is consistent with our results, where OSAS severity variables did correlate with LVMi normalized by height, but with a poorly relevant correlation coefficient ($r^2 = 0.039$). Nevertheless,

Table 4 Patient characteristics according to diastolic function class.

Characteristics	Normal ($n=118$)	Dysfunction grade I ($n=21$)	Dysfunction grade II ($n=48$)	Dysfunction grade III ($n=1$)
Clinical				
Men	101 (85.6)	18 (85.7)	38 (79.2)	0 (0)
Age (years)	50.0 (44.0—55.0)	60.0 (54.0—62.5)	52.0 (46.3—59.3)	43.0
Hypertension	85 (72)	20 (95.2)	42 (87.5)	1 (100)
Known hypertension	36 (30.5)	11 (11.2)	23 (47.9)	0 (0)
Masked hypertension	29 (24.6)	7 (33.3)	7 (14.6)	1 (100)
Nocturnal hypertension ($n=185$)[a]	63 (53.8)	12 (60.0)	37 (78.7)	0 (0)
Diurnal hypertension	69 (58.5)	15 (71.4)	35 (72.9)	1 (100)
Non-dipper ($n=185$)[a]	55 (46.6)	11 (52.4)	24 (50.0)	0 (0)
Diabetes	13 (11.0)	2 (9.5)	8 (16.7)	0 (0)
Metabolic syndrome	43 (36.4)	8 (38.1)	29 (60.4)	0 (0)
Current smoker	33 (28.0)	5 (23.8)	10 (20.8)	0 (0)
Obesity	63 (53.4)	9 (42.9)	32 (66.7)	1 (100)
BMI (kg/m^2)	30.9 (26.8—35.2)	28.1 (26.8—33.8)	32.1 (28.7—36.5)	45.4
Fasting glycaemia (mmol/L; $n=183$)[a]	5.2 (4.8—5.7)	5.4 (5.0—5.7)	5.5 (4.8—6.1)	5.4
Triglycerides (g/L; $n=184$)[a]	1.21 (0.93—1.70)	1.04 (0.88—1.67)	1.31 (1.03—2.00)	1.09
Creatinine (μmol/L; $n=185$)[a]	94 (85—103)	98 (89—108)	91 (83—101)	58
OSAS treatment, yes	105 (89.0)	19 (90.5)	40 (83.3)	1 (100)
Treatment with CPAP ($n=187$)[a]	99 (83.9)	18 (90.0)	40 (83.3)	1 (100)
AHI (events/hour)	47.5 (33.8—69.3)	45.0 (22.5—67.0)	49.5 (30.1—74.5)	121
Desaturation time (%; $n=180$)[a]	7 (2—23)	12 (5—33)	6 (0.1—30)	66
Epworth sleepiness score ($n=178$)[a]	10 (7—14)	12 (5—17)	11 (8—15)	5
24-hour heart rate (bpm)	74 (68—81)	74 (67—82)	73 (69—84)	78
24-hour SBP (mmHg)	129 (121—139)	134 (125—147)	131 (125—145)	125
24-hour DBP (mmHg)	78 (73—83)	83 (77—89)	79 (73—86)	72
Echocardiographic				
LVEF <50%	1 (0.8)	0	2 (4.2)	0
LVH (BSA; $n=169$)[a]	5 (4.7)	2 (10.5)	3 (7.0)	1 (100)
LVH ($height^{2.7}$; $n=169$)[a]	10 (9.4)	4 (21.0)	6 (13.9)	1 (100)
LVMi ($n=169$)				
Normalized by BSA	75.7 (65.9—87.8)	75.4 (60.1—91.5)	79.3 (70.4—94.0)	100.4
Normalized by $height^{2.7}$	35.2 (30.3—43.2)	36.0 (28.4—44.9)	36.8 (32.0—46.4)	61.5
LVEDD (mm; $n=185$)[a]	51.0 (48.0—54.7)	48.9 (44.8—55.7)	52.0 (48.0—55.3)	50.0
LVESD (mm; $n=186$)[a]	32.9 (28.7—36.5)	32.8 (28.8—37.9)	33.2 (29.5—37.2)	34.0
RWT ($n=169$)[a]	0.34 (0.30—0.38)	0.37 (0.34—0.46)	0.36 (0.30—0.39)	0.43
LV geometry (BSA; $n=169$)[a]				
Normal	89 (84.0)	11 (57.9)	36 (83.7)	0
Concentric remodelling	12 (11.3)	6 (31.6)	4 (9.3)	0
Concentric hypertrophy	3 (2.8)	1 (5.3)	1 (2.3)	1 (100)
Eccentric hypertrophy	2 (1.9)	1 (5.3)	2 (4.7)	0

Table 4 (*Continued*)

Characteristics	Normal ($n = 118$)	Dysfunction grade I ($n = 21$)	Dysfunction grade II ($n = 48$)	Dysfunction grade III ($n = 1$)
LV geometry (height$^{2.7}$; $n = 169$)[a]				
Normal	84 (79.2)	10 (52.6)	33 (76.7)	0
Concentric remodelling	12 (11.3)	5 (23.8)	4 (9.3)	0
Concentric LVH	3 (2.8)	2 (10.5)	1 (2.3)	1 (100)
Eccentric LVH	7 (6.6)	2 (10.5)	5 (11.6)	0
LAA (cm^2; $n = 168$)[a]	17.6 (15.2–20.4)	18.2 (15.3–23.2)	18.1 (15.8–20.9)	18.0
LAV (mL/m^2; $n = 94$)[a]	22.3 (18.8–29.1)	22.1 (18.0–36.7)	23.7 (17.8–32.2)	–
Pulmonary hypertension ($n = 178$)[a]	5 (4.2)	2 (9.5)	4 (8.3)	0
Diastolic function variables				
Lateral e′ velocity ($n = 169$)[a]	0.12 (0.11–0.13)	0.07 (0.06–0.08)	0.08 (0.08–0.09)	0.09
E/A ratio	1.11 (0.94–1.29)	0.68 (0.58–0.74)	1.00 (0.91–1.16)	2.09
E-wave deceleration time ($n = 172$)[a]	183.7 (166.7–201.7)	203.5 (183.0–242.9)	179.7 (163.0–200.9)	145
E/e′ ratio ($n = 169$)[a]	6.1 (5.3–7.4)	8.6 (6.4–9.6)	8.5 (7.6–11.0)	10.9
pA-mA duration ($n = 156$)[a]	−34.3 (−47.0–−20.7)	−37.3 (−49.5–−9.7)	−26.7 (−44.3–−11.8)	–

Data are expressed as number (%) or median (interquartile range). BSA: body surface area; E/A: early/late diastolic mitral peak flow velocity ratio; E/e′: mitral early diastolic peak flow velocity/early diastolic velocity by TDI ratio; LAA: left atrial area; LAV: left atrial volume; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end systolic diameter; LVH: left ventricular hypertrophy; LVMi: left ventricular mass index; mA: late diastolic mitral pulse-wave velocity duration; pA: late diastolic pulmonary pulse-wave velocity duration; RWT: relative wall thickness.

[a] Only available for patients without missing data.

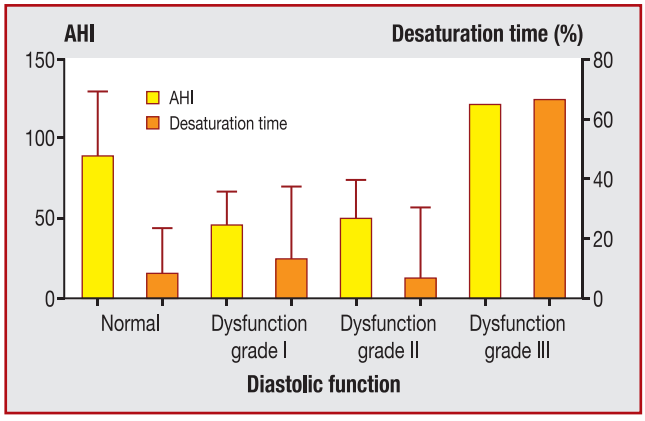

Figure 2. Apnoea-hypopnoea index and desaturation time across diastolic function classification. AHI: apnoea-hypopnoea index. Data are expressed as median (interquartile range).

we must mention several studies reporting a significant correlation between LVMi and severity of OSAS, even after adjustment for the main confounding factors [15,31] or in the specific context of heart failure [34]. Besides, from one study to another, the results of prevalent LVH may be very different depending on the methods used. Indeed, Noda et al. defined LVH according to interventricular septum or posterior wall thickness, without LVM calculation [32]. Likewise, several studies assessed LVH by LVMi normalized by BSA only [12–14,35]. Finally, LVH defined using LVMi normalized by height was more often eccentric than concentric, as found by Chami et al. [31], with a significant correlation between LV diameters and desaturation time but not AHI.

Left ventricular diastolic function

We found that 62.8% of our patients had normal LV diastolic function, assessed by a standardized approach, and that age was the only independent predictor of diastolic function. OSAS severity variables were not associated with diastolic dysfunction. Likewise, Spearman's correlation analysis did not show any correlation between different variables of diastolic function evaluation and AHI or desaturation time, suggesting that LV diastolic dysfunction is chiefly related to co-morbidities. These results are consistent with a previous large cross-sectional study by Niroumand et al., who found no significant difference in the E/A ratio between OSAS and non-OSAS patients [15]. However, in several other studies, associations were reported between OSAS severity and E/A ratio [35,36], A peak wave [36] or LA volume [37], with reversibility after a few months of CPAP treatment [33,37,38]. Furthermore, AHI was significantly correlated

Table 5 Predictors of left ventricular diastolic dysfunction.

	Univariate regression		Multivariable regression using LVMi normalized by BSA		Multivariable regression using LVMi normalized by height$^{2.7}$	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
LVMi, per 5 units increase						
Normalized by BSA	1.08 (0.99—1.18)	0.10	1.03 (0.94—1.14)	0.51	—	—
Normalized by height$^{2.7}$	1.16 (1.00—1.37)	0.06	—	—	1.08 (0.90—1.28)	0.42
Age	1.07 (1.03—1.11)	0.001	1.06 (1.02—1.10)	0.004	1.06 (1.02—1.10)	0.004
Male	0.68 (0.30—1.54)	0.36	—	—	—	—
Hypertension, yes	2.50 (1.14—5.51)	0.023	1.88 (0.81—4.40)	0.14	1.79 (0.75—4.28)	0.19
Hypertension, known	3.01 (1.32—6.89)	0.009	—	—	—	—
Hypertension, masked	1.70 (0.66—4.41)	0.28	—	—	—	—
Diurnal hypertension, yes	1.71 (0.86—3.37)	0.12	—	—	—	—
Nocturnal hypertension, yes (n = 166)	2.02 (1.02—3.98)[a]	0.043	—	—	—	—
Non-dipper, yes (n = 166)	1.28 (0.68—2.42)[a]	0.44	—	—	—	—
Diabetes, yes	1.46 (0.59—3.61)	0.41	—	—	—	—
Metabolic syndrome, yes	1.57 (0.84—2.95)	0.16	—	—	—	—
Current smoker, yes	0.80 (0.38—1.66)	0.54	—	—	—	—
BMI, per unit increase	1.00 (0.95—1.05)	0.97	—	—	—	—
AHI, after log transformation	0.88 (0.52—1.48)	0.62	—	—	—	—
Desaturation time, after log transformation (n = 161)	0.97 (0.78—1.19)[a]	0.76	—	—	—	—
24-hour heart rate, per 5 units increase	1.06 (0.90—1.23)	0.49	—	—	—	—
24-hour SBP, per 5 units increase	1.15 (1.02—1.31)	0.021	—	—	—	—
24-hour DBP, per 5 units increase	1.18 (0.97—1.44)	0.10	—	—	—	—

AHI: apnoea-hypopnoea index; BMI: body mass index; BSA: body surface area; DBP: diastolic blood pressure; OR (95% CI): odds ratio (95% confidence interval); SBP: systolic blood pressure.
[a] Only available for patients without missing data.

with LAA, which is a surrogate for diastolic function. However, the correlation coefficient was not sufficiently clinically relevant, and we did not observe such a correlation with desaturation time. Finally, to our knowledge, this is the first study to take a multivariable approach to the assessment of diastolic function in OSAS patients. Yet, OSAS patients often present normal LV systolic function or LVH, two conditions where the use of mitral inflow only is known to be inadequate because of a poor correlation between mitral flow pattern and haemodynamics [25].

Study limitations

This study has several limitations. First, it was a single-centre uncontrolled study. Our findings cannot necessarily be extrapolated to OSAS populations with less severe respiratory diseases, and severity of OSAS in this cohort did not allow to perform comparisons. However, the lack of a control group does not alter the demonstration of an independent relationship between LVMi (height) and hypertension on the one hand, and between diastolic dysfunction

and hypertension on the other. Moreover, the high severity of OSAS reported in this cohort makes us able to highlight a link between severity variables and diastolic dysfunction without powerfulness. Furthermore, the very low frequency in this population of co-morbidities known to be confounding factors that lead to diastolic dysfunction (diabetes, atrial fibrillation, LVH) allows us to focus on OSAS variables as an independent effect, and may partly explain our negative results.

Second, we did not consider the durations of OSAS or CPAP treatment. Thus, the low rate of LVH, and the prevalence of LV diastolic dysfunction and its correlation with OSAS, may be partly explained by a short duration of evolution in some cases and by a partial reversibility after CPAP treatment [33,38,39]. However, in most cases, patients were referred after the first sleep study, limiting the recruitment of patients with OSAS of long duration.

Lastly, as guidelines for diastolic function evaluation recommending the use of the average of septal and lateral e′ velocities were published in 2009, 4 years after the beginning of this study, only lateral mitral annular velocities were recorded.

Conclusions

In this observational study, we found a significant association between hypertension and LVMi corrected for height$^{2.7}$. We used a global standardized approach to assess the prevalence of diastolic dysfunction (37%) in a real-life cohort of OSAS patients. However, OSAS was not a predictor of LV diastolic dysfunction in multivariable analysis. Given that both LVH and diastolic dysfunction have important prognostic value, these results confirm the usefulness of a complete cardiovascular evaluation in patients with OSAS, but need to be supported by controlled comparative studies.

Acknowledgments

We thank Sophie Rushton-Smith for her editorial assistance in the preparation of this article.

Disclosure of interest

A.C. is a consultant and receives lecture fees from the companies AstraZeneca, Bayer Pharma, Boehringer-Ingelheim, Daiichi Sankyo, GlaxoSmithKline and Sanofi-Aventis. The other authors declare that they have no conflicts of interest concerning this article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.acvd.2015.03.006.

References

[1] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230—5.

[2] Malone S, Liu PP, Holloway R, Rutherford R, Xie A, Bradley TD. Obstructive sleep apnoea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. Lancet 1991;338:1480—4.

[3] Hung J, Whitford EG, Parsons RW, Hillman DR. Association of sleep apnoea with myocardial infarction in men. Lancet 1990;336:261—4.

[4] Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. Am J Cardiol 1983;52:490—4.

[5] Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA 2000;283:1829—36.

[6] Weitzenblum E, Krieger J, Apprill M, et al. Daytime pulmonary hypertension in patients with obstructive sleep apnea syndrome. Am Rev Respir Dis 1988;138:345—9.

[7] Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005;353:2034—41.

[8] Bradley TD, Floras JS. Sleep apnea and heart failure: part I: obstructive sleep apnea. Circulation 2003;107:1671—8.

[9] Lorell BH, Carabello BA. Left ventricular hypertrophy: pathogenesis, detection, and prognosis. Circulation 2000;102:470—9.

[10] Wachtell K, Palmieri V, Gerdts E, et al. Prognostic significance of left ventricular diastolic dysfunction in patients with left ventricular hypertrophy and systemic hypertension (the LIFE Study). Am J Cardiol 2010;106:999—1005.

[11] Milani RV, Lavie CJ, Mehra MR, Ventura HO, Kurtz JD, Messerli FH. Left ventricular geometry and survival in patients with normal left ventricular ejection fraction. Am J Cardiol 2006;97:959—63.

[12] Arias MA, Garcia-Rio F, Alonso-Fernandez A, Mediano O, Martinez I, Villamor J. Obstructive sleep apnea syndrome affects left ventricular diastolic function: effects of nasal continuous positive airway pressure in men. Circulation 2005;112:375—83.

[13] Dursunoglu D, Dursunoglu N, Evrengul H, et al. Impact of obstructive sleep apnoea on left ventricular mass and global function. Eur Respir J 2005;26:283—8.

[14] Kim SH, Cho GY, Shin C, et al. Impact of obstructive sleep apnea on left ventricular diastolic function. Am J Cardiol 2008;101:1663—8.

[15] Niroumand M, Kuperstein R, Sasson Z, Hanly PJ. Impact of obstructive sleep apnea on left ventricular mass and diastolic function. Am J Respir Crit Care Med 2001;163:1632—6.

[16] Lauer MS, Anderson KM, Kannel WB, Levy D. The impact of obesity on left ventricular mass and geometry. The Framingham Heart Study. JAMA 1991;266:231—6.

[17] Jain A, Avendano G, Dharamsey S, et al. Left ventricular diastolic function in hypertension and role of plasma glucose and insulin. Comparison with diabetic heart. Circulation 1996;93:1396—402.

[18] Lee M, Gardin JM, Lynch JC, et al. Diabetes mellitus and echocardiographic left ventricular function in free-living elderly men and women: the Cardiovascular Health Study. Am Heart J 1997;133:36—43.

[19] Mansia G, De Backer G, Dominiczak A, et al. 2007 ESH-ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Blood Press 2007;16:135—232.

[20] Hanley AJ, Wagenknecht LE, D'Agostino Jr RB, Zinman B, Haffner SM. Identification of subjects with insulin resistance and beta-cell dysfunction using alternative definitions of the metabolic syndrome. Diabetes 2003;52:2740—7.

[21] Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in

clinical research. The report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22:667—89.
[22] Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989;2:358—67.
[23] de Simone G, Daniels SR, Devereux RB, et al. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. J Am Coll Cardiol 1992;20:1251—60.
[24] Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. Eur J Echocardiogr 2006;7:79—108.
[25] Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107—33.
[26] Berger M, Haimowitz A, Van Tosh A, Berdoff RL, Goldberg E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. J Am Coll Cardiol 1985;6:359—65.
[27] Masuyama T, Kodama K, Kitabatake A, Sato H, Nanto S, Inoue M. Continuous-wave Doppler echocardiographic detection of pulmonary regurgitation and its application to noninvasive estimation of pulmonary artery pressure. Circulation 1986;74:484—92.
[28] Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol 1989;129:125—37.
[29] Cuspidi C, Facchetti R, Bombelli M, Sala C, Grassi G, Mancia G. Differential value of left ventricular mass index and wall thickness in predicting cardiovascular prognosis: data from the PAMELA population. Am J Hypertens 2014;27:1079—86.
[30] Baguet JP, Nadra M, Barone-Rochette G, Ormezzano O, Pierre H, Pepin JL. Early cardiovascular abnormalities in newly diagnosed obstructive sleep apnea. Vasc Health Risk Manag 2009;5:1063—73.
[31] Chami HA, Devereux RB, Gottdiener JS, et al. Left ventricular morphology and systolic function in sleep-disordered breathing: the Sleep Heart Health Study. Circulation 2008;117:2599—607.
[32] Noda A, Okada T, Yasuma F, Nakashima N, Yokota M. Cardiac hypertrophy in obstructive sleep apnea syndrome. Chest 1995;107:1538—44.
[33] Koga S, Ikeda S, Urata J, Kohno S. Effect of nasal continuous positive airway pressure in men on global left ventricular myocardial performance in patients with obstructive sleep apnea syndrome. Am J Cardiol 2008;101:1796—800.
[34] Damy T, Paulino A, Margarit L, et al. Left ventricle remodelling is associated with sleep-disordered breathing in non-ischaemic cardiopathy with systolic dysfunction. J Sleep Res 2011;20:101—9.
[35] Usui Y, Takata Y, Inoue Y, et al. Coexistence of obstructive sleep apnoea and metabolic syndrome is independently associated with left ventricular hypertrophy and diastolic dysfunction. Sleep Breath 2012;16:677—84.
[36] Kepez A, Niksarlioglu EY, Hazirolan T, et al. Early myocardial functional alterations in patients with obstructive sleep apnea syndrome. Echocardiography 2009;26:388—96.
[37] Romero-Corral A, Somers VK, Pellikka PA, et al. Decreased right and left ventricular myocardial performance in obstructive sleep apnea. Chest 2007;132:1863—70.
[38] Koga S, Ikeda S, Nakata T, Yasunaga T, Maemura K. Effects of nasal continuous positive airway pressure on left ventricular concentric hypertrophy in obstructive sleep apnea syndrome. Intern Med 2012;51:2863—8.
[39] Shivalkar B, Van de Heyning C, Kerremans M, et al. Obstructive sleep apnea syndrome: more insights on structural and functional cardiac alterations, and the effects of treatment with continuous positive airway pressure. J Am Coll Cardiol 2006;47:1433—9.