Original Article

Left ventricular diastolic dysfunction in patients with obesity hypoventilation syndrome

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Background: Obesity hypoventilation syndrome (OHS) can be complicated by several cardiovascular conditions. We assessed the prevalence and factors associated with left ventricular diastolic dysfunction (LVDD) in patients with OHS.

Methods: In this prospective observational study, all consecutive OHS patients referred to the sleep disorders clinic between January 2002 to December 2016 were included (n=113). Demographic data, echocardiography, sleep parameters, arterial blood gases (ABGs), and lung functions were recorded.

Results: Of 113 patients with OHS who participated, 76 patients (67%) had LVDD. More than two-thirds had grade 1 LVDD. Median body mass index (BMI) was 42.8 kg/m^2. Median $PaCO_2$ was 55.8 mmHg. Median apnea hypopnea index (AHI) was 52 (25–38.5). Eighty-four (75.7%) patients were hypertensive, and 60 (54.1%) were diabetic. To minimize the effect of fluctuations in intrathoracic pressure during the obstructive respiratory events on the cardiac function, 38 OHS patients with mild to moderate OSA (AHI <30) were identified. Twenty-seven (71%) had LVDD. When compared to OHS patients without LVDD, patients with LVDD had higher BMI (47.4±6.5 versus 41.5±4.5, P=0.009). Hypertension was more common in OHS patients with LVDD than without LVDD (89.3% versus 54.5%, P=0.03). Correlation analysis revealed that hypertension (r=–0.37, P=0.016) had significant correlations with LVDD.

Conclusions: Diastolic left ventricular dysfunction is prevalent among OHS patients even in the absence of severe OSA. Hypertension and obesity were significantly more common in patients with LVDD. Assessment of diastolic dysfunction should be included in the initial evaluation of OHS patients to encourage the early institution of therapy.

Keywords: Obstructive sleep apnea; pulmonary hypertension (PH); cardiovascular disease; hypercapnia

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Introduction

Obesity is a serious health concern worldwide (1). It is associated with an increased risk of cardiovascular diseases, diabetes, chronic pain, asthma, and obesity hypoventilation syndrome (OHS) (2,3). The exact pathophysiological mechanisms responsible for OHS have yet to be clearly defined. Proposed theories include complex interactions among impaired respiratory mechanics, abnormal central ventilatory control, possible sleep-disordered breathing, and neurohormonal aberrancies (4).

OHS patients have a progressive disease course, high health care utilization, and higher risks of hospitalization and death (5,6). The associated respiratory, metabolic, hormonal, and cardiovascular impairments in OHS can lead to lower quality of life and increased morbidity and mortality (7). Only a few studies have assessed cardiac complications in patients with OHS, and these focused mainly on right ventricular dysfunction and pulmonary hypertension (PH) (8,9).

Several recent reports have suggested that left ventricular dysfunction in patients with OHS could be mainly due to diastolic dysfunction (10,11). However, these studies were retrospective and included a small sample size. We hypothesize that left ventricular diastolic dysfunction (LVDD) is common among patients with OHS. Therefore, we designed this study to more comprehensively assess the prevalence, clinical characteristics, and factors associated with LVDD in patients with OHS.

Methods

This study is a prospective observational study conducted between January 2002 and December 2016 at King Saud University Medical City, a tertiary-care University hospital in Riyadh, Saudi Arabia. The local ethics committee approved the study, and informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki. We included all consecutive patients (≥18 years old) who met the diagnostic criteria of OHS, body mass index (BMI) >30 kg/m², daytime awake $PaCO_2$ >45 mmHg, and in whom hypoventilation was not primarily due to a chronic lung disease, chest wall deformity, medications, a neuromuscular disorder, or a known congenital or idiopathic central alveolar hypoventilation syndrome (12). None of the studied patients was in acute hypercapnic respiratory failure at the time of echocardiography. Hypertensive patients were defined as those who had a documented history of hypertension or were on antihypertensive treatment. Diabetes was defined as HbA1C >6.5 or being on antidiabetic agents. Exclusion criteria included patients with chronic liver or renal disease, recent myocardial infarction, atrial fibrillation, and moderate or severe valvular heart disease.

Demographic data including co-morbidities, smoking history, and BMI were recorded. Additionally, all patients underwent transthoracic echocardiography, pulmonary function test (PFT), and arterial blood gases (ABGs) after 15 minutes of rest while the subjects were awake, seated, and breathing room air. The blood gases were analyzed using a GEM® Premier™ 4000 analyzer (Instrumentation Laboratory, Lexington, MA, USA).

Polysomnography

Patients underwent a type-I attended overnight sleep study with neurological, cardiac, and respiratory monitoring using Alice® diagnostic equipment (Philips, Respironics Inc., Murrysville, PA, USA) (13,14). Scoring was performed manually according to the American Academy of Sleep Medicine (AASM) scoring criteria (15). The desaturation index was defined as the number of desaturation events (≥3% decrease in oxygen saturation from the pre-event baseline) per hour of sleep.

Echocardiography

Echocardiography was carried out using a Philips iE33 (Philips Ultrasound Bothell, WA, USA) cardiac ultrasound machine, with an electronic transducer of variable frequency and capacity for two-dimensional (2D), M-mode, continuous, and pulsed wave Doppler and color images. The examination was performed in M-mode with 2D guidance in the long axis of the left parasternal view. Left ventricular internal end-diastolic and end-systolic diameters, as well as interventricular septum and posterior wall thicknesses, were measured over five consecutive cycles (16). Systolic function was assessed by the left ventricular ejection fraction according to the Teicholz formula (17). Left ventricular diastolic function was evaluated by transmitral Doppler using the pulsed-Doppler technique with 2D guidance in the apical four-chamber view. Left ventricular diastolic function can be measured by flow parameters including the early (E) and late (A) diastolic filling velocities, the E/A ratio, and the E deceleration time (DT) from an apical four-chamber view using the pulsed-Doppler technique with 2D guidance. The transmitral E wave is related to the time course of active left ventricular relaxation, which produces a pressure gradient from the left atrium through the left ventricular inflow tract to the left ventricular apex (18,19). Therefore, the early left ventricular diastolic filling is affected by the interaction of left atrial compliance and the rate of ventricular relaxation. The peak E velocity may increase by minimal left ventricular diastolic pressure caused by rapid left ventricular relaxation, or elevated left atrial pressure (the cause of high E/A ratios in cardiac disease) (19,20). Impaired left ventricular relaxation denotes grade

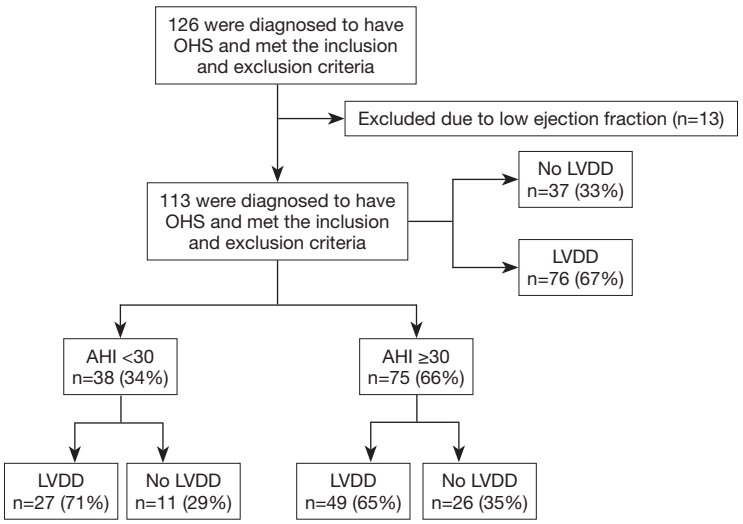

Figure 1 A flowchart of the distribution of recruited patients. OHS, obesity hypoventilation syndrome; LVDD, left ventricular diastolic dysfunction; AHI, apnea hypopnea index.

1 diastolic dysfunction, grade 2 is pseudonormalization, and grades 3 and 4 are diagnosed when there is restrictive physiology (21). All echocardiographic tests were performed by the same experienced echocardiographer.

Statistical analysis

Continuous variables of the study population characteristics were expressed as the mean ± standard deviation or as the median (lower percentile, upper percentile) if normality assumption failed. Categorical data were expressed as n (%). Comparisons between two categorical variables were made using the chi-square test. Continuous data were compared using student *t*-test or Mann Whitney U-test depending on data distribution. A P value less than 0.05 was considered statistically significant. Pearson's correlation coefficient was used to assess the association of study parameters with diastolic dysfunction. Statistical Package for Social Sciences software (SPSS version 22; IBM Corporation, Armonk, NY, USA) was used for data analysis and management.

Results

A total of 126 patients met the inclusion and exclusion criteria and agreed to participate. Eleven patients had moderately reduced ejection fraction (EF) (35–40%) and two had severe left ventricular systolic dysfunction (EF 25–30%). These patients (n=13) were excluded. *Figure 1* shows the distribution of the recruited patients.

In the finally included group (n=113), the mean age of the participants was 57.8±13.3 yrs. The median BMI was 42.8±11.5 kg/m^2. Males represented 29.2% (n=33). The median arterial partial pressure of carbon dioxide ($PaCO_2$) was 55.68±13.35 mmHg. Approximately, 35% of patients were on positive airway pressure therapy at the time of cardiac evaluation, 84 (74.3%) patients were hypertensive and 60 (53.1%) were diabetic (*Table 1*).

Of the 113 patients with OHS, 76 patients (67%) were found to have LVDD. Of those with LVDD, more than two-thirds (67%) had grade 1 diastolic dysfunction, and the rest had grades 2 and 3 (26% and 7%, respectively) (*Figure 2*).

To minimize the effect of fluctuations in intrathoracic pressure during obstructive respiratory events on cardiac function, we did a subgroup analysis based on the apnea hypopnea index (AHI). Thirty-eight OHS patients with mild to moderate OSA (AHI <30) were identified (*Table 2*). Twenty-seven (71%) of them had LVDD; whereas 49 (65%) of patients with severe OSA (AHI ≥30) had LVDD (*Figure 1*). In the subgroup of OHS patients with mild to moderate OSA, OHS patients with LVDD had higher BMI compared to OHS patients without LVDD (47.4±6.5 kg/m² versus 41.5±4.5 kg/m², P=0.009). In addition, hypertension was more common in OHS patients with LVDD than without LVDD (89.0% versus 54.5%, P=0.03). There were no significant differences in age, partial pressure of oxygen or carbon dioxide, or in measured sleep parameters. Time spent with oxygen saturation SpO_2 <90% and <95% was longer in the OHS with LVDD group; however, it did not

Table 1 Demographics and general information of the study group

Variable	Mean ± SD/n (%), total (n=113)
Males	33 (29.2)
Age (years)	57.8±13.3
BMI (kg/m^2)	42.8 (32.2–50)
$PaCO_2$ (mmHg)	55.8 (31.1–37.2)
PaO_2 (mmHg)	60.6±13.1
FVC (% predicted)	52.2±21.1
FEV1 (% predicted)	52.3±19.8
AHI (events/hr)	52 (25–38.5)
AHI-NREM (events/hr)	51.9 (3–20.9)
AHI-REM (events/hr)	53.1±40.8
Sleep latency (mins)	12.8 (0–18.9)
WASO (mins)	35 (16–87.5)
Desaturation index (desaturations/hr)	39.7 (2.1–16)
Arousal index (arousals/hr)	49.9 (0.1–12.2)
Time with SpO_2 <90% (mins)	93.3 (36.4–100)
Time with SpO_2 <95% (mins)	100 (90–100)
Hypertension	84 (74.3)
Diabetes	60 (53.1)
Ischemic heart disease	13 (11.5)
Chronic kidney disease	9 (8.0)
Hypothyroidism	26 (23.0)
Using PAP at the time of echocardiography	40 (35.4)
Medications	
ACE inhibitors and ARBs	28 (24.8)
β-blocker	11 (9.7)
Calcium-channel antagonists	23 (20.4)
Diuretics	38 (33.6)
Bronchodilator agents	31 (27.4)
Anti-platelet agents	44 (39.0)
Warfarin	5 (4.4)
Sildenafil	2 (1.8)
Home O_2	27 (24.0)

$PaCO_2$, partial pressure carbon dioxide; PaO_2, partial pressure oxygen; FVC, forced vital capacity; FEV1, forced expiratory volume in first second; BMI, body mass index; AHI, apnea hypopnea index; REM, rapid eye movement; NREM, non-rapid eye movement; WASO, wakefulness after sleep onset; SpO_2, blood oxygen saturation; PAP, positive airway pressure; SD, standard deviation.

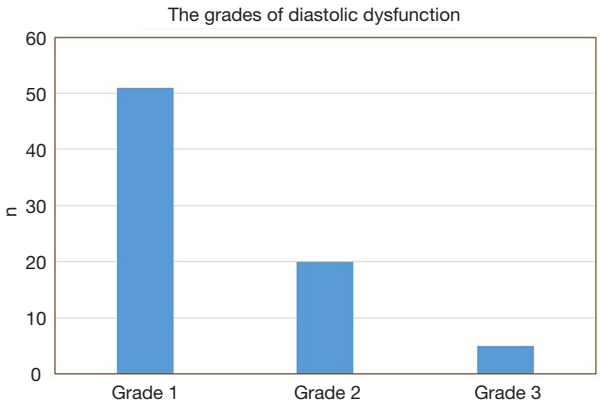

Figure 2 The grades of left ventricular diastolic dysfunction among patients with obesity hypoventilation syndrome.

reach statistical significance (*Table 2*). Correlation analysis revealed that hypertension (r=–0.37, P=0.016) significantly correlated with LVDD in OHS patients with mild OSA (*Table 3*).

Discussion

Although cardiac dysfunction is a known comorbidity of OHS, only a limited number of studies have addressed this topic. Our study is the largest prospective study to assess the prevalence of LVDD among OHS patients, and to study LVDD in patients with OHS and mild to moderate OSA. We observed that the prevalence of LVDD was 67% in patients with OHS, and 71% in a sub-group of OHS patients with AHI <30, which is much higher than the prevalence reported in the public ranging from 11–34% (22,23). The majority of LVDD in OHS patients were mild, grade 1. Our results are in agreement with the findings of Alawami *et al.*, who retrospectively reviewed 47 patients with OHS and reported left ventricular systolic dysfunction in 25% and LVDD in 60% of patients (10).

In the present study, the median AHI of patients with OHS was 52 events/hr. LVDD and left ventricular remodeling have been frequently reported in patients with OSA, and left ventricular dysfunction correlates with the severity of OSA and AHI (24). The reported prevalence of diastolic dysfunction in OSA is approximately 23% (25,26). Large swings in intrathoracic pressure in OSA patients may increase sympathetic activity and surges in blood pressure (27). Recurrent forced inspiration against the occluded airway during apnea episodes results in excessive negative intrathoracic pressure. Additionally,

Table 2 Clinical characteristics of obesity hypoventilation syndrome patients with AHI <30/hr with and without left ventricle diastolic dysfunction (LVDD)

Variable total (n=38)	Mean ± SD/n (%)/median (25th–75th percentile)		P value
	No LVDD (n=11)	With LVDD (n=27)	
Gender (male)	2 (18.2)	7 (25.9)	1.000
Age (years)	55±17.8	57.6±13.5	0.632
BMI (kg/m^2)	41.5±4.5	47.4±6.5	0.009
$PaCO_2$ (mmHg)	56.4±11.4	57.3±11.1	0.831
PaO_2 (mmHg)	61.7±11.9	61.4±13.1	0.937
FVC (% predicted)	41.8±17.8	48.1±19.4	0.481
FEV1 (% predicted)	43±15.5	46.9±16.6	0.620
AHI (events/hr)	12.3±8.5	13.9±8.7	0.622
AHI-NREM (events/hr)	11±8.6	11±8.5	0.998
AHI-REM (events/hr)	19.7±18.2	31.1±27.5	0.253
Sleep latency (mins)	14 (7–36.9)	10.8 (6–51.9)	0.747
WASO (mins)	82.3±83.5	34.5 (8.8–84.3)	0.218
Desaturation index (desaturations/hr)	6 (2.0–41.0)	12 (5.3–27.1)	0.525
Arousal index (arousals/hr)	21.2±10.3	23.9±12.5	0.541
Time with SpO_2 <90% (mins)	47.7±39	75.5 (1–99.2)	0.769
Time with SpO_2 <95% (mins)	67.8±37.6	99.5 (42.8–100)	0.373
Hypertension (%)	6 (54.5)	24 (89.0)	0.031
Diabetes (%)	6 (54.5)	18 (67.0)	0.263
Ischemic heart disease (%)	1 (9.1)	3 (11.1)	1.000
Chronic kidney disease (%)	1 (9.1)	1 (3.7)	0.524
Hypothyroidism (%)	4 (36.4)	1 (3.7)	0.023

$PaCO_2$, partial pressure carbon dioxide; PaO_2, partial pressure oxygen; FVC, forced vital capacity; FEV1, forced expiratory volume in first second; BMI, body mass index; AHI, apnea hypopnea index; REM, rapid eye movement; NREM, non-rapid eye, movement; WASO, wakefulness after sleep onset; SpO_2, blood oxygen saturation; SD, standard deviation.

these pressure swings lead to an increased venous return to the right ventricle with an overload of the right ventricle, which pushes the interventricular septum to shift to the left, resulting in reduced left ventricular end-diastolic volume (28). In addition to increased blood pressure, these factors collectively cause diastolic dysfunction (29,30). In order to minimize the effect of fluctuations in intrathoracic pressure during the obstructive respiratory events on the cardiac function, we opted to analyze the subgroup of OHS patients with AHI <30 (31).

The prevalence of LVDD in OHS patients with mild to moderate OSA was high (71%), indicating that other factors, apart from repetitive obstructive events, contribute to the development of LVDD. Morbid obesity is a well-known risk factor for heart failure, even in the absence of other cardiovascular risk factors such as ischemic heart disease, hypertension, and diabetes (32,33). The incidence of obesity was reported to be 41.4% in patients discharged with a diagnosis of heart failure with preserved ejection fraction (34). Additionally, various neurohormonal and metabolic abnormalities associated with obesity, such as hyperinsulinemia, hyperleptinemia, as well as activation of the renin-aldosterone-angiotensin system and the sympathetic nervous system are thought to be responsible

Table 3 Correlation of diastolic dysfunction with study parameters

Variable	r	P value
Gender (male)	0.083	0.611
Age (years)	0.083	0.632
BMI (kg/m^2)	0.212	0.269
$PaCO_2$ (mmHg)	0.036	0.831
PaO_2 (mmHg)	–0.013	0.937
FVC (% predicted)	0.142	0.481
FEV1 (% predicted)	0.102	0.620
AHI (events/hr)	0.085	0.622
AHI-NREM (events/hr)	0.000	0.998
AHI-REM (events/hr)	0.224	0.253
Sleep latency (mins)	–0.067	0.755
WASO (mins)	–0.275	0.227
Desaturation index (desaturations/hr)	0.107	0.533
Arousal index (arousals/hr)	0.119	0.489
Time with SpO_2 <90% (mins)	0.093	0.588
Time with SpO_2 <95% (mins)	0.215	0.207
Hypertension	–0.369	0.016
Diabetes	0.205	0.226
Ischemic heart disease	0.043	0.798
Chronic kidney disease	–0.102	0.539
Hypothyroidism	–0.431	0.010

$PaCO_2$, partial pressure carbon dioxide; PaO_2, partial pressure oxygen; FVC, forced vital capacity; FEV1, forced expiratory volume in first second; BMI, body mass index; AHI, apnea hypopnea index; REM, rapid eye movement; NREM, non-rapid eye, movement; WASO, wakefulness after sleep onset; SpO_2, blood oxygen saturation; r, correlation coefficient.

for cardiac remodeling, left ventricular hypertrophy and dysfunction, and altered left ventricular morphology (35). It is postulated that the inflammatory state and oxidative stress that develop with morbid obesity can lead to an increase in left ventricular mass including left ventricular internal diastolic chamber size and left ventricular wall thickness. Left ventricular mass correlates with BMI and mortality (21,35). In this study, there was a significant difference in BMI between OHS subjects with and without LVDD when severe OSA was excluded (*Table 2*).

Furthermore, sleep disordered breathing in itself can increase the risk of cardiovascular disease. A strong association with cardiovascular disease was found among obese patients with sleep apnea compared to matched controls of obese patients without sleep apnea (10,32,33). The chronic sustained hypoxemia that occurs in OHS causes sympathetic activation, systemic inflammation, oxidative stress, and metabolic abnormalities (31). These in turn result in left ventricular remodeling and left ventricular hypertrophy, which are the cardinal feature of diastolic dysfunction (36,37). On the other hand, hypercapnia exerts direct effects on cardiac myocytes due to an increase in acidity that results in depressed cardiac contractility and inhibition of glycolysis and the Krebs cycle (38,39).

Hypertension was more common in patients with LVDD than those without LVDD (*Table 2*). The chronic hypoxemia that occurs in OHS patients can cause a reflex elevation of the arterial blood pressure. This in turn may increase the work load of the heart and lead to left ventricular hypertrophy (38). Hypertension is a known risk factor for LVDD. Hypertension was diagnosed in 55–86% of a cohort of 2,843 patients with heart failure with preserved ejection fraction (39,40). Furthermore, respiratory acidosis that results from hypercapnia stimulates the sympathetic nervous system. The resultant tachycardia can further impair left ventricular filling and worsen LVDD (38).

Limitations of this study include the absence of a matched control group of obese patients; however, it is difficult to find middle-age morbidly obese patients without sleep disordered breathing. Another limitation is the fact that echocardiographic assessment of LVDD does not have very high specificity and positive predictive value, and the specificity may be compromised by conditions such as atrial fibrillation and mitral valve disease, which commonly cause left atrial dilatation (19,41). Future studies should use more advanced methods for cardiac assessments, such as cardiac MRI and left ventricular mass measurements (42).

In conclusion, LVDD is common among patients with OHS even without significant OSA. The identification of risk factors for LVDD may provide further insight into possible mechanisms underlying cardiac complications in this population. This will facilitate early recognition and provision of treatment. Targeting these risk factors may thus help to attenuate the development of LVDD.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study protocol was approved by the institutional review board at King Saud University (ethics approval number is 11/3235/IRB), and informed consent was obtained from all of the participants prior to inclusion in this study.

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