Evaluation of left ventricular function in obese patients with obstructive sleep apnea by three-dimensional speckle tracking echocardiography

Jingwen Zhao 1 · Weihong Li 1 · Jianli Wang 2 · Zixuan Hu 2 · Yongwei Huang 2 · Yongzhen Zhang 1 · Liqiang Zhang 2

Received: 25 February 2022 / Accepted: 23 May 2022 / Published online: 24 June 2022
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Abstract
Both obstructive sleep apnea (OSA) and obesity can cause myocardial remodeling and cardiac insufficiency via corresponding pathophysiological pathways. Therefore, it is speculated that the superposition of OSA and obesity may cause more severe impairment of cardiac function. The objective of our study was to evaluate the early changes of left ventricular systolic function in obese patients with OSA with three-dimensional speckle tracking echocardiography (3D-STE). This study was conducted with 33 obese OSA, 46 non-obese OSA, and 20 healthy subjects. Demographic, biochemical, and Polysomnography (PSG) data were collected, and their relation with the left ventricular strain was measured and analyzed with 3D-STE. The left ventricular strain was significantly worse in the OSA group compared to the control group \((P < 0.05)\). The global longitudinal strain (GLS) was significantly worse obese group compared to non-obese OSA group \((P < 0.05)\). The GLS value positively correlated with body mass index (BMI) \((r = 0.406, P < 0.001)\), apnea–hypopnea index (AHI) \((r = 0.610, P < 0.001)\) and homeostasis model assessment of insulin resistance (HOME-IR) \((r = 0.431, P < 0.001)\) in patients with OSA, as well as high sensitivity C-reactive protein (hs-CRP) \((r = 0.394, P < 0.001)\). Multiple linear regression analysis showed BMI and AHI were predictors of GLS. In OSA patients, the myocardial strain was impaired before the damages in left ventricular ejection fraction, suggesting that the left ventricular systolic function is damaged early. The coexistence of obesity and OSA can lead to severe impairment of cardiac function through mechanisms such as hypoxia and insulin resistance.

Keywords Obesity · Obstructive sleep apnea · Left ventricular dysfunction · Three-dimensional speckle tracking echocardiography

Introduction
Obstructive sleep apnea (OSA) is a severe disorder in which an individual repeatedly starts and stops breathing during their sleep. It results from the complete or partial obstruction of the upper airway during sleep that causes intermittent hypoxia and carbon dioxide retention [1, 2]. Obesity is one of the important pathogenic factors of OSA. Studies have shown that both OSA and obesity can cause myocardial remodeling and early impairment of cardiac function through sympathetic nervous system activation, insulin resistance, systemic inflammation, and oxidative stress [3, 4]. When obesity and OSA coexist, it is speculated that the superposition of the pathophysiological effects of the two may lead to more severe impairment of cardiac function. However, the subclinically impaired cardiac function is easily overlooked, especially in OSA patients with obesity. As the association of OSA or obesity with adverse cardiac remodeling is high, an early assessment of the cardiac function would aid in reducing cardiovascular morbidity and mortality. As such, it is imperative that the physicians identify such patients with early signs of changes in cardiac function. But the assessment of cardiac function over the early stage of cardiac insufficiency in obese OSA patients has not yet been reported as far as we know. Initial impairments in cardiac function in obesity or OSA may be subtle, such as alterations in the regional contractile strain due to aberrant...
pressure in the myocardium, to the extent that they are challenging to detect on routine echocardiography.

Three-dimensional speckle tracking echocardiography (3D-STE) is an advanced imaging technique that tracks the movement of the myocardium based on ultrasonic speckles in full-volume 3D images. It provides a comprehensive assessment of the myocardial deformation from the perspective of the whole and segment. This enables early and sensitive detection of systolic and diastolic myocardial capacity changes compared to conventional echocardiography. 3D-STE can give parameters on myocardial deformation such as longitudinal strain, area strain, torsional strain for evaluating cardiac function [5, 6]. In OSA patients with no apparent symptoms of cardiac dysfunction, the early stage of impaired cardiac function largely remains undetected by conventional echocardiography. This study proposes to identify subclinical left ventricular dysfunction in obese OSA patients by using 3D-STE and provide a reference for early treatment.

Methods

Study population

We performed a single center, prospective study on consecutive patients with OSA who underwent sleep monitoring at the Sleep Medicine Center of Peking University Third Hospital from July 2018 to December 2019. 91 OSA patients were chosen but 12 subjects were excluded because of poor echocardiographic quality or uncompleted sleep monitoring. Finally 79 OSA patients were carried out for our study. OSA was determined following the diagnostic criteria of obstructive sleep apnea underlined in the International Classification of Sleep–Third edition(ICSD-3) 2014 [7]. Exclusion criteria included previously diagnosed patients with heart failure, coronary artery disease, valvular disease, cardiomyopathy, arrhythmia, chronic obstructive/restrictive pulmonary disease, thyroid dysfunction (including hypothyroidism, hyperthyroidism), already treated with CPAP, and poor image quality of echocardiography. 20 healthy subjects who underwent sleep monitoring at about the same period to exclude OSA were selected as the control group. The Ethics Committee of Peking University Third Hospital (Ethical approval number M2017152) approved the study. The study was performed following the ethical standards of the Declaration of Helsinki and its later amendments. Informed consent forms were obtained from all the individuals enrolled in the study.

Demographic data

Demographic characteristics of the participants were measured. Patients with BMI > 28 kg/m² (Chinese BMI cutoff for obesity) were classified as obese [8], and those below were defined as the non-obese grouped likewise. Since metabolic abnormalities are common to obesity and sleep apnea, which may be mediators of cardiac insufficiency, we measured metabolic indices at the same time. For example, the levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), high sensitivity C-reactive protein (hs-CRP), glycated hemoglobin (HbA1c), fasting glucose, and fasting insulin of all participants were estimated. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the formula [fasting glucose (mmol/l) × insulin (µU/ml)]/22.5 [9]. Ambulatory blood pressure monitoring (ABPM) was performed in all patients. The patients who had 24 h ABP ≥ 130/80 mmHg, awake ABP ≥ 135/85 mmHg, and/or sleep ABP ≥ 120/70 mmHg with ambulatory blood pressure monitoring were considered hypertensive.

Polysomnography (PSG)

All subjects were monitored using the Polywin Polysomnography (PSG) system (Philips, USA). Caffeine, sedatives, hypnotic drugs, and alcohol were not allowed on the day of the examination. The sleep state was determined by three-channel electroencephalography, two-channel electrooculography, one-channel submental electromyography, and bilateral tibia electromyography. To detect OSA events, oral and nasal airflow, thoracic cage and abdominal respiratory motion, nasal air pressure, and arterial oxyhemoglobin saturation were used. Respiratory movements were measured with chest and abdominal belts, nasal pressure with a pressure sensor and oxygen saturation was determined using an oximeter probe. Sleep stages, respiratory events, thermistor, electrocardiography were scored by trained sleep technicians following the criteria laid down by the American Academy of Sleep Medicine (AASM) in 2012 [10]. A reduction in the airflow by at least 90% lasting ≥ 10 s was defined as an apnea event. Hypopnea was defined as cessation of airflow by at least 30% with at least 3% oxygen desaturation in the preceding 30 s, and a reduction in chest wall movement and/or arousal. The average number of apnea plus hypopnea events/hour of sleep defined the apnea–hypopnea index (AHI). Individuals with an AHI ≥ 5 were classified as OSA, whereas those with an AHI < 5 were classified as control subjects. Apnea severity was classified as mild OSA (AHI 5-14), moderate OSA (AHI 15-29), and severe OSA (AHI ≥ 30).
Three-dimensional speckle tracking echocardiography (3D-STE)

We used GE Vivid E9 color Doppler echocardiography diagnostic instrument with M5Sc and 4 V-D probe of 2–4 Hz. It was additionally equipped with an EchoPAC PC workstation and 4D Auto LVQ strain image analysis software to capture images. The frame rate ranged from 50 to 70 frame/s. Standard echocardiographic parameters recorded were left atrial diameter (LAD), left atrial area (LAA), left ventricular end-diastolic diameter (LVEDD), E/A. And the left ventricular ejection fraction (LVEF) was acquired using the modified biplane Simpson method from the apical 4- and 2-chamber views. The European Association of Echocardiography/American Society of Echocardiography (EAE/ASE) criteria was followed for all standard 2D and Doppler images and parameters. When we performed 3D speckle tracking analysis, the LV endocardial and epicardial borders were automatically detected by the 4D Auto LVQ strain image analysis software, after which we would manually adjust the borders if unsatisfactory with image tracking. In addition, the 17-segment model according to the American Heart Association standard for myocardial segmentation was used. 3D Image quality was considered good if just only 0–1 segment was poorly visualized; if ≥ 2 segments were not successfully delineated, the image is considered to be of poor quality which was regarded as unsuitable for analysis, and the patient will be excluded. Then we calculated LV strain parameters with analysis time of approximately 5 min per sample, which included three-dimensional echocardiographic global longitudinal strain (3DE-GLS), three-dimensional echocardiographic global circumferential strain (3DE-GCS), three-dimensional echocardiographic global radial strain (3DE-GRS), three-dimensional echocardiographic global area strain (3DE-GAS). The GLS, GAS, and GCS measurements had negative values, and GRS had positive values. The negative values of GLS, GAS, and GCS indicate the myocardium’s shortening, thinning, or counterclockwise rotation. The positive values of GRS represent the lengthening, thickening, or clockwise rotation of the myocardium. Thus, lower negative strain values numerically represent the greater degree of cardiac deformation [5]. All echocardiographic recorders and analyzers were blinded to the group throughout the entire study. To ensure the stability and accuracy of the three-dimensional strain parameters, we took three readings of each parameter and calculated the average.

Reproducibility analysis

The intra-observer variabilities of 3D values were assessed by one experienced sonographer. And intra-observer measures were performed at least 1 week apart in random order. The observer was blinded to previous measurements and the clinical data of the patients participating in this study.

Statistical analysis

Statistical analysis was performed using SPSS software version 20.0. Normality test was performed by Kolmogorov–Smirnov test. Measurement data with normal distribution were expressed as mean ± standard error. A t-test was performed for comparison between two groups, while ANOVA was used to compare multiple groups with LSD for post hoc analysis. The measurement data of skewed distribution were represented by M(P25, P75). The Mann–Whitney U test was used to compare two groups, and the Kruskal–Wallis test was used to compare multiple groups. Relative numbers expressed count data, and comparison was performed by χ² test. Pearson’s correlation analysis was performed for data with normal distribution and Spearman correlation analysis for skewed distribution. Multiple linear regression was used to analyze the predictive factors of three-dimensional strain. Reliability was assessed using the intraclass correlation coefficient (ICC). P < 0.05 was considered statistically significant.

Results

Clinical and demographic characteristics in different groups

This study was conducted with a total of 99 subjects. Of them, 79 subjects had mild to severe OSA, and 20 were healthy and without OSA. They were considered as the control group. The OSA subjects consisted of 12 cases of mild OSA, 29 cases of moderate OSA, and 38 cases of severe OSA. The OSA group was further divided into 33 obese patients and 46 non-obese patients. The BMI, T-G, fasting blood glucose, and HbA1c in the OSA group were significantly higher than those of the control group, while the HDL-c was lower (P < 0.05). Within the OSA group, the hs-CRP, fasting blood glucose, HbA1c, and insulin, and HOME-IR were higher in obese OSA patients compared to those of non-obese OSA patients (P < 0.05). The PSG results showed that the total recorded time spent below 90% oxygen saturation (Ts90%) was significantly longer in the obese group compared to the non-obese OSA group. Demographic characteristics of patients between different subgroups were presented in Tables 1, 2, 3 and 4.
Parameters of myocardial strain by 3D-STE

In 3D-STE, OSA patients’ GLS, GCS, GAS, and GRS were more damaged than the control group \((P < 0.05)\). Intra-group analysis showed that the strain of patients with moderate to severe OSA was worse than that of the control group \((P < 0.05)\). The GLS of the obese OSA group was worse than that of the non-obese group \((P < 0.05)\). In the same weight group, the

| Table 1 | Clinical and demographic characteristics in control and OSA groups |
|---------|---------------------------------------------------------------------|
| Variables | Control group \((n = 20)\) | OSA group \((n = 79)\) | \(P\)-value |
| Sex (men:women) | 6:14 | 67:12 | 0.001 |
| Age | 37.5(33.0,42.0) | 40.0(34.3,48.0) | 0.110 |
| BMI \((\text{kg/m}^2)\) | 24.49(21.94,24.97) | 27.17(25.35,29.66) | \(0.006^{bc}\) |
| TC \((\text{mmol/l})\) | 4.64(4.34,4.75) | 4.72(4.12,5.21) | 0.153 |
| TG \((\text{mmol/l})\) | 1.03(0.81,1.07) | 1.60(1.25,2.39) | \(0.002^{bc}\) |
| HDL-c \((\text{mmol/l})\) | 1.34(1.10,1.54) | 1.02(0.90,1.17) | \(0.001^{ab}\) |
| LDL-c \((\text{mmol/l})\) | 2.77(2.50,3.02) | 3.14(2.52,3.62) | 0.057 |
| Hs-CRP \((\text{mg/l})\) | 0.87(0.52,2.13) | 1.02(0.60,2.09) | 0.815 |
| Fasting glucose \((\text{mmol/l})\) | 5.15(5.00,5.50) | 5.40(5.10,6.00) | 0.003 |
| HbA1c \(\%\) | 5.50(5.27,5.60) | 5.70(5.50,6.00) | 0.001 |
| LDL-c \((\text{mmol/l})\) | 8.50(7.50,15.00) | 12.15(8.48,16.48) | 0.199 |
| HOME-IR | 1.89(1.73,4.54) | 3.14(2.03,3.36) | 0.112 |
| 24 h mean SBP \((\text{mmHg})\) | 119.18 ± 12.75 | 120.89 ± 11.59 | 0.655 |
| 24 h mean DBP \((\text{mmHg})\) | 78(70,88) | 78(73,86) | 0.866 |
| Daytime mean SBP \((\text{mmHg})\) | 125(111,130) | 123(116,133) | 0.984 |
| Daytime mean DBP \((\text{mmHg})\) | 80(74,91) | 81(76,89) | 0.902 |
| Night-time mean SBP \((\text{mmHg})\) | 109.27 ± 14.74 | 111.73 ± 12.16 | 0.547 |
| Night-time mean DBP \((\text{mmHg})\) | 67(62,80) | 70(64,78) | 0.709 |
| AHI | 3.00(1.10,4.60) | 29.2(19.98,46.95) | \(<0.001^{bcdef}\) |
| LSao2 | 92%(89%,93%) | 80%(70%,80%) | \(<0.001^{bcdef}\) |
| Ts90% | 0.0%(0.0%,0.0%) | 5.3%(1.0%,19.0%) | \(<0.001^{bcdef}\) |
| LAD (mm) | 30.41 ± 3.78 | 33.93 ± 3.89 | 0.006 |
| LAA (mm²) | 16(13,17) | 17(15,19) | 0.030 |
| LVEDD (mm) | 46.40(43.90,47.50) | 47.45(44.85,50.22) | 0.095 |
| E/A | 1.31(0.90,1.80) | 1.17(0.92,1.44) | 0.067 |
| LAP (mmHg) | 8.06(6.08,8.3) | 8.06(6.09,8.0) | 0.343 |
| LVEF (%) | 73.06(68.07,74.0) | 69.5(66.0,73.0) | 0.117 |
| GLS | –16.24 ± 4.60 | –12.78 ± 3.83 | \(0.035^{bcde}\) |
| GCS | –15.19 ± 3.67 | –13.14 ± 3.46 | \(0.032^{bcde}\) |
| GAS | –27.15 ± 5.83 | –22.57 ± 5.35 | \(0.035^{bcde}\) |
| GRS | 38.34(35.63,53.08) | 32.83(26.75,41.75) | \(0.039^{bcde}\) |
| 3D-LVEF (%) | 57.86 ± 4.55 | 56.12 ± 4.58 | 0.139 |

BMI body mass index, TC total cholesterol, TG triglyceride, HDL-c high density lipoprotein cholesterol, LDL-c low-density lipoprotein cholesterol, hs-CRP high sensitivity C-reactive protein, HOMA-IR homeostasis model assessment of insulin resistance, ABPM ambulatory blood pressure monitoring, SBP systolic blood pressure, DBP diastolic blood pressure, AHI apnea–hypopnea index, LSao2 minimum oxygen saturation, Ts90% the total recorded time spent below 90% oxygen saturation, LAD left atrial diameter, LVEDD left ventricular end diastolic diameter, LAP left atrial pressure, LVEF left ventricular ejection fraction, 3D-STE 3D speckle tracking echocardiography, GLS global longitudinal strain, GCS global circumferential strain, GAS global area strain, GRS global radial strain

\( ^{a}p < 0.05 \) control versus mild OSA,

\( ^{b}p < 0.05 \) control versus moderate OSA,

\( ^{c}p < 0.05 \) control versus severe OSA

\( ^{d}p < 0.05 \) mild OSA versus moderate OSA

\( ^{e}p < 0.05 \) mild OSA versus severe OSA

\( ^{f}p < 0.05 \) moderate OSA versus severe OSA
more severe the OSA, the worse the strain. All the data are listed in Tables 1, 2, 3 and 4. A example of strain image was shown in Fig. 1.

We calculated ICC and standard error of measurement and displayed in Table 5. 3D-STE strain parameters demonstrated good reliability[ICC: 0.836–0.918].

**Correlation analysis of 3D-STE strain parameters in OSA patients**

Negative GLS, an indicator of impaired longitudinal strain was positively correlated with BMI(r = 0.406, P < 0.001), AHI(r = 0.610, P < 0.001) and HOME-IR.
There were no linear correlations ($P > 0.05$) with age, gender, and blood pressure (including 24 h mean SBP and DBP). The results indicated that the larger the BMI, the more deteriorated the OSA condition, and the more severe the insulin resistance and inflammatory status, the more severe was the longitudinal strain damaged. There were no linear correlations between GCS, GAS, GRS and BMI, AHI, HOME-IR, hs-CRP, age, gender, blood pressure separately ($P > 0.05$).

The positive results of correlation analysis are shown in Fig. 2.

**Multiple linear regression of 3D-STE strain parameters in OSA patients**

Multiple linear regression analysis was performed using GLS as dependent variable in patients with OSA.

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**Table 3 Clinical and demographic characteristics in obese patients with different severity of OSA**

| Variables                  | Mild-moderate OSA (n = 17) | Severe OSA (n = 16) | $P$-value |
|----------------------------|----------------------------|---------------------|-----------|
| Sex (man:woman)            | 15:2                       | 15:1                | 0.582     |
| Age (yrs)                  | 42.35 ± 11.90              | 41.88 ± 8.61        | 0.451     |
| BMI(kg/m$^2$)              | 30.37 ± 2.47               | 31.23 ± 3.48        | 0.419     |
| T-C(mmol/l)                | 4.65 ± 0.72                | 4.92 ± 0.77         | 0.297     |
| T-G(mmol/l)                | 1.71(1.43,2.76)            | 1.69(1.39,2.37)     | 0.843     |
| HDL-c(mmol/l)              | 1.00 ± 0.22                | 1.00 ± 0.14         | 0.947     |
| LDL-c(mmol/l)              | 3.04 ± 0.83                | 3.32 ± 0.75         | 0.302     |
| hs-CRP(mg/l)               | 1.24(0.65,2.47)            | 2.85(1.07,4.00)     | 0.105     |
| Fasting glucose(mmol/l)    | 5.65 ± 0.70                | 6.28 ± 1.21         | 0.086     |
| HbA1c(%)                   | 5.73 ± 0.46                | 6.27 ± 0.64         | 0.010     |
| Fasting insulin(µU/ml)     | 14.69 ± 6.01               | 18.11 ± 6.82        | 0.143     |
| HOME-IR                   | 3.66 ± 1.57                | 5.13 ± 2.33         | 0.040     |
| 24 h mean SBP(mmHg)        | 123.64 ± 8.94              | 127.00 ± 14.25      | 0.452     |
| 24 h mean DBP(mmHg)        | 79.07 ± 7.30               | 85.80 ± 10.86       | 0.062     |
| Daytime mean SBP(mmHg)     | 126.93 ± 9.48              | 131.93 ± 13.69      | 0.261     |
| Daytime mean DBP(mmHg)     | 81.79 ± 7.13               | 89.33 ± 10.80       | 0.036     |
| Night-time mean SBP(mmHg)  | 116.50 ± 9.37              | 116.53 ± 16.69      | 0.995     |
| Night-time mean DBP(mmHg)  | 73.21 ± 8.29               | 78.27 ± 11.81       | 0.197     |
| AHI                        | 20.27 ± 5.92               | 55.07 ± 20.22       | 0.010     |
| LSaO2                      | 83.0% ± 6.4%               | 72.2% ± 8.9%        | 0.107     |
| Ts90%                      | 5.0%(1.0%,28.5%)           | 28.0%(4.7%,38.7%)   | 0.073     |
| LAD(mm)                    | 34.70(33.25,37.75)         | 35.20(32.73,37.70)  | 0.971     |
| LA/A(mm$^2$)               | 19.00(15.50,21.00)         | 18.00(16.25,19.00)  | 0.562     |
| LVEDD(mm)                  | 49.05 ± 3.39               | 49.30 ± 4.20        | 0.853     |
| E/A                        | 1.24(1.04,1.53)            | 1.09(0.85,1.23)     | 0.105     |
| LAP(mmHg)                  | 9.0(6.0,10.0)              | 8.5(6.0,9.8)        | 0.373     |
| LVEF                       | 69.0% ± 5.8%               | 70.4% ± 4.0%        | 0.419     |
| GLS                        | −13.88 ± 2.97              | −8.18 ± 1.57        | < 0.001   |
| GCS                        | −13.78 ± 3.84              | −12.96 ± 3.30       | 0.513     |
| GAS                        | −22.63 ± 6.05              | −20.77 ± 4.71       | 0.335     |
| GRS                        | 35.07 ± 11.38              | 30.92 ± 10.04       | 0.276     |
| 3D-LVEF(%)                 | 57.77 ± 5.80               | 53.31 ± 5.12        | 0.026     |

BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; ABPM, ambulatory blood pressure monitoring; SBP, systolic blood pressure; DBP, diastolic blood pressure; AHI, apnea–hypopnea index; LSaO2, minimum oxygen saturation; Ts90%, the total recorded time spent below 90% oxygen saturation; LAD, left atrial diameter; LAD, left atrial area; LVEDD, left ventricular end diastolic diameter; LAP, left atrial pressure; LVEF, left ventricular ejection fraction; 3D-STE, 3D speckle tracking echocardiography; GLS, global longitudinal strain; GCS, global circumferential strain; GAS, global area strain; GRS, global radial strain.
and BMI, HOME-IR, AHI, and hs-CRP as independent variables. The residuals from the model carried out conformed to a normal distribution. The results showed that BMI $\beta = 0.282$, 95% CI (0.077, 0.488), $P = 0.008$ was a predictor of GLS in OSA patients, as well as AHI $\beta = 0.093$, 95%CI (0.058, 0.128), $P < 0.001$. The results of multiple linear regression analysis are given in Table 6.

### Discussion

Strain and strain rate are measures of changes in shape and therefore represent deformations, which are closely related to myocardial contractility. Three-dimensional speckle tracking imaging, a quantitative approach which allows the simultaneous evaluation of cardiac strain and...
3D reconstruction of the LV volume changes frame-by-frame, can detect the change of cardiac contractility early and sensitively. Cardiac magnetic resonance is the gold standard for evaluating the global or local myocardial function. The 3D-STE correlates well with cardiac magnetic resonance in measuring myocardial strain. In addition, it has the advantage of being easier to handle, and cheaper [6, 11]. Torrent-Guasp et al. [12] found that various arrangements of myocardial fibers in anatomy determine the form of myocardial movement in different directions corresponds to GLS, GRS, GCS and GAS. Previous studies have confirmed that patients with OSA or obesity generally exhibit impaired LV diastolic function with normal LVEF, which can reflect the normal systolic function of the left ventricle [13]. In our study we found that OSA patients’ left ventricular strain was worse than the control group. Within the OSA group, the GLS of obese patients was significantly damaged compared to the non-obese patients. Consistent with the results of previous studies [14–16], the impaired LV myocardial strain observed in our study points out that though the LVEF is still normal, subclinical LV systolic insufficiency has already developed in patients with OSA. In addition, we found that the subclinical left ventricular systolic function was more significantly impaired in OSA patients who also suffered from obesity, which was rarely illustrated in previous studies.

Studies have shown that OSA increases the risk of hypertension, arrhythmia, coronary heart disease, and heart failure [17]. The ARIC-SHHS study showed that residents with OSA already had subclinical myocardial damage without any discernible cardiovascular and cerebrovascular diseases [18]. Recurrent apnea and hypoxemia at night in OSA patients result in sympathetic hyperactivity and decreased parasympathetic excitability. It will exacerbate oxidative stress, systemic inflammation, and vascular endothelial dysfunction, which lead to insulin resistance, abnormal lipolysis, and myocardial metabolic disorders. The significantly
higher values of the biochemical parameters in the OSA group compared to the control and that of the OSA obese group compared to the non-obese measured in the present study reflect severe metabolic abnormalities and systemic inflammatory in OSA patients, particularly in those with obesity.

The OSA is also accompanied by cardiac hypertrophy and myocardial fibrosis, which are essential in myocardial remodeling [19]. The elevated blood pressure level in patients with OSA increases the left ventricular afterload. Hypoxia and carbon dioxide retention exaggerate swings in intrathoracic pressure during the obstructive episode, which leads to an increase in return blood volume and left ventricular preload [20]. At the molecular level, the contraction and relaxation of the heart are highly energy-dependent, 90% of which are provided by the oxidative phosphorylation in

Table 6  Multiple linear regression of 3D-STE strain parameters in OSA patients

| GLS | Unstandardized β | SE | Standardized β | 95% CI | t | P-value |
|-----|-----------------|----|----------------|-------|---|---------|
| Constants | −24.846 | 2.659 | −9.343 | <0.001 | |
| BMI | 0.282 | 0.103 | 0.265 | 0.077–0.488 | 2.738 | 0.008 |
| HOME-IR | 0.315 | 0.215 | 0.150 | −0.113–0.743 | 1.467 | 0.147 |
| AHI | 0.093 | 0.018 | 0.492 | 0.058–0.128 | 5.273 | <0.001 |
| Hs-CRP | −0.002 | 0.046 | −0.004 | −0.094–0.090 | −0.047 | 0.963 |

Multiple linear regression was used to analyze the predictive factors of three-dimensional strain. *P* <0.05 was considered as statistically significant.

**BMI** body mass index, **HOME-IR** homeostasis model assessment of insulin resistance, **AHI** apnea–hypopnea index, **GLS** global longitudinal strain, **Hs-CRP** high-sensitivity C-reactive protein.
studies have shown that the strain is impaired in asymptomatic obese patients, several speckle-tracking echocardiography function [22]. Although the LVEF tends to be normal in hypertrophy, left atrium volume increase, and diastolic dysfunctions have proved that obesity leads to left ventricular heart failure. Large-scale clinical trials and basic observations as important determinants of the development of heart failure. Large-scale clinical trials and basic experiments have proved that obesity leads to left ventricular hypertrophy, left atrium volume increase, and diastolic dysfunction [22]. Although the LVEF tends to be normal in obese patients, several speckle-tracking echocardiography studies have shown that the strain is impaired in asymptomatic obese patients, both children and adults [23–27]. There is an accumulation of intracellular triglycerides and lipids over the hearts of obese people. The myocardial substrate selection due to obesity favors fatty acid oxidation, leading to lipotoxicity and myocardial dysfunction [28]. The thickening of epicardial adipose tissue (EAT) leads to excessive activation of macrophages, releasing pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. It results in activated pro-inflammatory signaling pathways that further aggravates organ dysfunction [29]. In addition, the activation of the renin–angiotensin–aldosterone system with stimulation of the sympathetic nervous system in obese patients increases left ventricular afterload even in normotensive-obese patients, leading to cardiac remodeling and myocardial fibrosis.

Our study showed that the LV strain was associated with the degree of insulin resistance in addition to OSA and obesity. Previous studies have shown that insulin resistance is one of the major causes of myocardial injury, and both obesity and OSA can cause subclinical myocardial dysfunction by insulin resistance [30]. The degree of OSA correlates with the severity of insulin resistance. Intermittent hypoxemia and oxidative stress in OSA patients have been critical factors leading to insulin resistance. It has been suggested that ATP synthesis in pancreatic islet β cells is affected by hypoxemia and then insulin secretion is suppressed. In addition, it reduces the phosphorylation of insulin receptor tyrosine kinases and thereby reduces the effect and sensitivity of insulin receptors [31], resulting in insulin resistance. A high HOMA-IR index is one of the characteristics of metabolic disorders in obese patients. Insulin resistance increases cardiac toxicity by altering myocardial metabolism. The toxicity and the increased release of insulin-related growth factors activate the sympathetic and RAAS systems that result in myocardial remodeling [32]. In addition, insulin resistance is independently associated with impaired GLS, leading to LV hypertrophy and damaged myocardial function over time [33].

Various mechanisms closely related to obesity, such as insulin resistance, oxidative stress, systemic inflammation, visceral fat accumulation, and dyslipidemia, may also occur as OSA-associated manifestations. Obesity and OSA interlink mutually and exist as complex, interleaved vicious cycles. It eventually leads to overlapping and potential effects of organ crosstalk [34]. It is widely known that both obesity and OSA can independently lead to cardiovascular complications. Our study further elucidated that the coexistence of obesity and OSA might have a synergistic effect on myocardial strain compared to the presence of OSA alone. In patients with OSA, if combined with obesity, the myocardial strain damage will be further exacerbated. This is also valid for obese patients suffering from OSA. As discussed previously, although obesity contributes to the development of cardiac insufficiency through several mechanisms, many of them overlap with those of OSA. Unlike OSA, obesity is also characterized by an increase in systemic blood volume and cardiac output, which alters hemodynamics, increasing LV pressure and volume, and eventually changes the strain of the myocardium. Obesity tends to coexist with OSA. Our study suggested that OSA and obesity might have a superimposed effect on the early impairment of left ventricular systolic function. Therefore, for the sake of improving the cardiovascular prognosis, it is crucial to focus early on the management of obese OSA patients in which subclinical LV impairment are detected. OSA can be treated in a variety of modalities, including continuous positive airway pressure (CPAP), which is considered to be the optimal treatment, active weight loss, oral appliance therapy, and surgical approaches. These treatments can reduce the severity of OSA and improve quality of life [35]. However evidence, mostly observational, exists showing that CPAP and weight loss lead to improvements in cardiac structure and function. Yet we do not know the independent or additive effect of CPAP and weight loss on these variables, we recommend that obese OSA patients with an indication for CPAP wear ventilator applications at night and undergo weight management [36, 37].

We conducted a study to assess myocardial strain in obese patients with OSA using 3D-STE. Similar to 3D-STE, 2D-STE performs well in measuring myocardial strain.
2D-STE is favourably used for tracking of the endocardial boundary and tested for the quantification of LV volume and function. But 2D strain analysis is subject to the out-of-plane motion of the speckles during the cardiac cycle due to its 2D nature. 3D-STE using a volumetric approach is capable of overcoming the limitation mostly by tracking motion in all three dimensions and eliminating the need for geometric modelling. 3D-STE also can eradicate the errors caused by the use of foreshortened views in 2D-STE. Indeed, as we have noticed, 3D-STE demonstrates high reproducibility, lower variability levels, and consumes less time in acquisition and analysis. Hence it was chosen to be a reliable measurement tool used in our study. Yet it is also limited to arrhythmia, along with a significant dependence on the quality of the ultrasound window particularly endocardial boundary delineation.

**Study Limitations**

Our study has several limitations. A comparison should also be drawn between obese but not OSA patients with the obese and OSA patient. None of the controls were even overweight. Most of the patients are obese, which may affect the accuracy of speckle-tracking and data analysis due to unclear image quality restricted by ultrasonic transmission conditions. As an observational study, the results may be affected by confounding factors such as blood pressure levels. Definitive conclusions regarding LV myocardial deformation could not be drawn as our sample size is small. As such, the reliability and accuracy of our research results need to be further verified by expanding the sample size. And our study applied an extensive exclusion criteria, so the results may not be extrapolated to patients with comorbidities which could act as confounding factors and influence measurements. In addition, the observed substantial improvement in LV strain after interventional treatment of obese and OSA patients needs to be confirmed in future studies with a larger cohort of patients having OSA with or without obesity.

**Conclusion**

Our study shows that the myocardial strain of OSA patients is impaired before the left ventricular ejection fraction damages. This indicates that the left ventricular systolic function of patients with OSA is damaged at the early stage. When obesity coexists with OSA, the pathophysiological effects of both superimpose, possibly leading to more severe impairment of cardiac function through mechanisms such as hypoxia and insulin resistance.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s10554-022-02660-6.

**Author contributions** LZ and YZ put forwarded the idea for this article and guided the implementation of the whole project. WL and JW assisted with project implementation and patient enrollment, and Dr. WL performed echocardiographic measurements. ZH and YH were responsible for baseline data collection, PSG monitoring, and reporting analysis. JZ was responsible for data collection and analysis and wrote the article. Dr. LZ critically revised the work. All authors read and approved the final manuscript.

**Funding** Not applicable.

**Data availability** All data generated or analyzed during this study are included in this published article and its supplementary information files.

**Code availability** Not applicable.

**Declarations**

**Conflict of interest** Not applicable.

**Consent to participate** All the subjects had given their written informed consent.

**Consent for publication** All the authors agreed to the publication of the manuscript.

**Ethical approval** The Ethics Committee of Peking University Third Hospital approved this study (M2017152).

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