Objective: Obstructive sleep apnea (OSA) is a prevalent condition that is increasingly recognized to be associated with cardiovascular disease. We aimed to investigate the subclinical systolic ventricular dysfunction of patients with OSA using novel speckle tracking echocardiographic (STE) techniques.

Methods: This study included 31 patients of polysomnography proven very severe OSA [Apnea Hypopnea Index (AHI) >40] and an equal number of matched population with no OSA as controls. All the study participants underwent a detailed conventional and tissue Doppler strain echocardiogram in addition to STE.

Results: There was no significant difference in conventional ventricular systolic function parameters including left ventricular (LV) ejection fraction, and myocardial performance index of left ventricle. Diastolic function was significantly reduced in patients with OSA as compared to controls. There was no difference in global circumferential strain or time to its peak between the two groups. However global longitudinal LV strain (GLS) was significantly reduced in patients with OSA (p < 0.01). Similarly time to peak longitudinal strain was prolonged in the OSA group as compared to controls. Segmental analysis revealed that the longitudinal strain abnormalities were more pronounced in the apical and mid segments of LV. AHI remained the only significant predictor of GLS in these patients.

Conclusion: Very severe OSA is associated with significant diastolic dysfunction as well as early systolic abnormalities as evidenced by abnormal global longitudinal strain. Sleep apnea severity as measured by AHI was the only significant predictor of abnormal longitudinal strain in these patients.

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myocardium including abnormal systolic strain even at a much earlier stage. We wished to study the abnormalities in ventricular strain of patients with OSA using the novel STE technique with a case control methodology.

2. Methods

2.1. Study population

Thirty one adult patients, who were newly diagnosed with very severe OSA and who were symptomatic due to the disease, were enrolled in the between January and December 2011, where very severe OSA was arbitrarily defined as having an apnea-hypopnea index of more than 40 events per hour in an overnight polysomnographic [PSG] test. Exclusion criteria included (a) central sleep apnea, (b) known structural heart disease including coronary artery disease (c) left ventricular (LV) dysfunction (Ejection fraction < 55%), (d) cardiac rhythm other than sinus (e) history of congestive heart failure (f) chronic lung disease (g) thyroid disorders (h) severe hypertension as labeled by a blood pressure of more than 160/100 mm Hg or the use of more than one antihypertensive agent and (h) prior use of continuous positive airway pressure (CPAP). An equal number of controls matched for age, sex, body mass index and hypertension were selected from among the relatives of patients attending the cardiology outpatient department and these were found to be normal in clinical and echocardiographic evaluation. Obstructive sleep apnea was ruled out in these patients using the Berlin sleep questionnaire.

All those patients in whom a satisfactory echo window was not obtained were also excluded from the study. Institutional Ethics Committee approval was acquired and informed consent was taken from all the study participants.

2.2. Study protocol

Patients who met the aforementioned inclusion and exclusion criteria were recruited and baseline demographic data was collected. A detailed clinical history was procured from all participants in the study followed by a comprehensive physical examination. The data collected included the nature of symptoms, duration of symptoms and functional limitation due to these symptoms and treatment history. Any comorbid illnesses including diabetes, hypertension, dyslipidemia and previous stroke were documented. Body weight, neck circumference and height were noted and body mass index and body surface area were computed using standard charts. All patients underwent a one-time detailed echocardiographic examination.

2.3. Polysomnography (PSG)

All patients underwent an overnight PSG in the sleep laboratory using standard techniques. Electroencephalogram, chin electromyogram, electrocardiogram, chest and abdominal respiratory movements and electrooculography recordings were made during the entire sleep duration. Oro-nasal airflow and arterial oxygen saturation (Sao2) were measured continuously using special thermistor sensors and pulse oximeter respectively. American Academy of Sleep Medicine definitions were used for measuring various sleep parameters: apnea was defined as a complete stoppage of inspiratory airflow for at least 10 s; hypopnoea, a significant decrease in airflow for at least 10 s associated with reduction in saturation of more than 4% from the baseline or on arousal of the patient; apnea/hypopnoea index (AHI) was defined as the number of apnoea and/or hypopnoea events per hour of sleep and OSA was diagnosed if the patient had AHI of five or more.

2.4. Transthoracic echocardiography

All patients underwent baseline comprehensive echocardiographic evaluation according to American Society of Echocardiography guidelines using Philips IE – 33 echocardiography machine (Philips Medical Systems, Andover, MA, USA). Echocardiography was performed in all standard views and stored in digital format for offline analysis (using Q lab, version 4.2, Philips Medical Systems) later. All measurements were drawn from 5 consecutive cycles and averaged.

The LV ejection fraction (LVEF) was acquired using the modified biplane Simpson method from the apical 4- and 2-chamber views. The left atrial (LA) volume was estimated from the area-length method from the 4- and 2-chamber views at the maximal atrial dimension and adjusted for the body surface area. The trans-mitral pulsed wave Doppler velocities were recorded from the apical 4-chamber view with a 2-mm Doppler sample placed between the tips of the mitral leaflets. Early (E) and late (A) wave velocities, E/A ratio and deceleration time were measured from the mitral inflow profile. Left ventricular myocardial performance index was calculated using Doppler echocardiography measurements across aortic valve as follows: (isovolumetric contraction time of the left ventricle + isovolumetric relaxation time of left ventricle)/aortic ejection time. Pulse-wave TDI obtained from the apical 4-chamber view with a 2-mm sample volume placed at the septal mitral annulus in order to assess Systolic (S’), early diastolic (E’), late diastolic (A’) velocities, and the mitral E/E’ ratio was derived using these values.

One cardiac cycle each from apical and short axis views was selected in order to measure two principal strains- longitudinal and circumferential- using two-dimensional speckle tracking imaging of the left ventricle. The endocardial border was, then, manually defined in this cardiac cycle frame by frame. The region of interest was drawn out to include the entire myocardium, which was then divided into six segments by the software for speckle tracking analysis. In addition to the two aforementioned strains, time to peak LV strain from the onset of QRS was also measured for both.

2.5. Intra- and inter-observer variability

The primary investigator repeated all the echo measurements of randomly selected eight OSA patients and five control subjects after a one month period to determine the intra-observer variability. All these measurements were then repeated by another observer in same study subjects to assess the inter-observer variability.

2.6. Statistical analysis

Continuous data sets have been expressed in mean±standard deviation and frequencies as percentages. Statistical analysis was done using SPSS version 18 for Microsoft windows software package. After checking for normality, t-test was used for calculating significance of the different variables. Categorical variables were compared using Fischer's exact test or chi square test as deemed appropriate. The relation of OSA severity with various echocardiographic parameters was assessed by Pearson correlation. Further, multiple linear regression was performed for the factors which were found to be significant in that analysis. Intraclass correlation coefficient and Chronbach’s alpha was calculated to assess the inter- and intra-observer reproducibility. A p value of <0.05 was considered significant.
3. Results

A total of 38 patients with OSA and 33 control subjects were evaluated initially for inclusion in this study. However, owing to inadequate image window, six OSA patients and two controls were excluded from the final analysis. One patient in the OSA group was excluded due to intermittent atrial fibrillation noted during 24 h Holter study. 31 patients were analyzed in each group in the final analysis. Baseline characteristics of patients with OSA and the control subjects as well as the polysomnography data of the former are presented in Table 1. Both the groups were well matched with regard to age, sex, body mass index (BMI), presence of diabetes and hypertension and the systolic blood pressure. However, the neck circumference was significantly higher in the patients in OSA group as compared to control subjects (39.2 +/− 3.1 versus 36.5 +/− 2.8, p < 0.01). The mean AHI of patients with OSA recruited in this study was 74.3 (+/−13.2), signifying that our research included patients with very severe form of the disease.

Details of conventional and tissue Doppler echocardiographic parameters for both the groups are charted in Table 2. There was no difference in the LV ejection fraction by biplane Simpson method between the two groups, however, the LV mass and indexed LA volumes were significantly higher in patients with severe OSA when compared to the control population. There was no significant difference in conventional Doppler indices like Mitral E/A, deceleration time and Left ventricular MPI between the two groups. Patients in the OSA group had lower E’ velocity and higher E/E', suggesting delayed relaxation and elevated filling pressures.

Left ventricular strain assessed by speckle tracking echocardiographic techniques are shown in detail in Table 3. Global longitudinal strain was considerably decreased in patients with severe OSA as compared to controls. Furthermore, segmental analysis of longitudinal strain was done after dividing LV into basal, mid and apical segments. This parameter was significantly lower in all the three segments in patients of OSA. The difference in longitudinal strain was much more pronounced in apical and mid segments than in the basal segments with a clear gradation from base to apex of the left ventricle. Time to peak global longitudinal strain was also prolonged in OSA patients in comparison to the control population (p = 0.02). On segmental analysis, the time to peak systolic strain in longitudinal direction was significantly prolonged in the apical segments as well as in the mid segments but the difference was not statistically significant in the basal segments. Unlike longitudinal strain parameters, there was no difference noted between the two groups with regard to circumferential systolic strain of the LV as well as the time to peak circumferential strain.

### Table 1
Baseline characteristics of patients with severe OSA and the control population.

|                | Severe OSA (n = 31) | Control (n = 31) | P value |
|----------------|---------------------|-----------------|---------|
| **Age**        | 48.3 (9.6)          | 46.2 (7.4)      | 0.35    |
| **Males (%)**  | 24 (77.4)           | 23 (74.2)       | 0.77    |
| **BMI**        | 29.2 (4.1)          | 27.6 (3.1)      | 0.11    |
| **Neck Circumference (cm)** | 39.2 (3.1) | 36.5 (2.8) | <0.01  |
| **Diabetes (%)** | 5 (16.1)           | 4 (12.9)        | 0.72    |
| **Hypertension (%)** | 17 (54.8)        | 15 (48.4)       | 0.61    |
| **Systolic BP (mm Hg)** | 146.1 (13.9) | 142.3 (12.9)  | 0.27    |
| **AHI**        | 74.3 (33.2)         | –               |        |
| **Micro arousal index** | 66.8 (19.1)     | –               |        |
| **Desaturation index** | 50.4 (10.1)     | –               |        |
| **Mean Nocturnal SpO2 (%)** | 89.5 (3.9)       | –               |        |

Continuous data are expressed in mean (Standard deviation) and frequencies are expressed as number (percentage).

OSA: Obstructive sleep apnea, BMI: Body mass index, BP: Blood Pressure, AHI: Apnea hypopnea index, SpO2: Oxygen saturation.

### Table 2
Conventional and tissue Doppler parameters of patients in both the groups.

|                | Severe OSA (n = 31) | Control (n = 31) | P value |
|----------------|---------------------|-----------------|---------|
| **LV EF (%)** | 66.2 (3.5)          | 65.2 (3.4)      | 0.30    |
| **IVSd (mm)** | 11.8 (1.3)          | 11.2 (1.2)      | 0.05    |
| **PWd (mm)**  | 11.4 (1.3)          | 10.7 (1.1)      | 0.05    |
| **LVM (g/m^2)** | 98.5 (13.5)     | 92.8 (9.8)      | 0.04    |
| **LA volume (mL)** | 306.5 (2.5) | 283.0 (4.7)     | 0.02    |
| **Mitral E/A** | 11 (0.2)            | 12.0 (2.2)      | 0.09    |
| **Mitral DT (ms)** | 162.8 (21.9)   | 153.5 (20.0)    | 0.12    |
| **LV MPI**    | 0.43 (0.09)         | 0.41 (0.04)     | 0.12    |
| **E' (cm/s)** | 9.2 (2.1)           | 10.6 (1.1)      | 0.01    |
| **E/E'**      | 9.69 (2.6)          | 8.44 (1.6)      | 0.03    |

Data are expressed in mean (Standard deviation).

OSA: Obstructive sleep apnea, LV: Left ventricle, EF: ejection fraction, IVSd: Interventricular septum dimension, PWd: Posterior wall dimension, LVM: Left ventricular mass, LAVI: Left atrial volume index, E/A: Ratio between early and late diastolic mitral inflow velocities, MPI: Myocardial performance index, E': Tissue doppler diastolic anular velocity, E/E': ratio between early diastolic mitral inflow velocity and early diastolic anular velocity.

### Table 3
Two dimensional speckle strain values of patients with severe OSA and the control population.

|                | Severe OSA (n = 31) | Control (n = 31) | P value |
|----------------|---------------------|-----------------|---------|
| **GLS (%)**   | −15.1 (1.8)         | −19.1 (1.6)     | <0.01   |
| **LS basal (%)** | −15 (1.9)         | −17 (1.7)       | 0.02    |
| **LS mid (%)** | −15 (2.3)          | −18 (1.8)       | <0.01   |
| **LS apical (%)** | −16 (2.5)        | −20 (1.7)       | <0.01   |
| **Tp GLS (ms)** | 397.1 (30.3)     | 379.3 (29.9)    | 0.02    |
| **Tp LS basal (ms)** | 384.9 (31.9) | 366.8 (28.3)    | 0.06    |
| **Tp LS mid (ms)** | 395.1 (27.2)    | 375.3 (29.9)    | <0.01   |
| **Tp LS apical (ms)** | 411.6 (28.4)    | 383.5 (29.9)    | <0.01   |
| **GCS (%)**   | −21 (1.4)           | −21 (1.6)       | 0.11    |
| **Tp GCS (ms)** | 394.50 (23.6)    | 379.26 (32.3)   | 0.14    |

Data are expressed in mean (Standard deviation).

OSA: Obstructive sleep apnea, GLS: Global longitudinal strain, LS basal: Longitudinal strain of basal left ventricular segments, LS mid: Longitudinal strain of middle left ventricular segments, LS apical: Longitudinal strain of apical left ventricular segments, Tp: Time to peak strain in milliseconds, GCS: Global longitudinal strain.

The relationships of various systolic strain parameters with AHI are shown in Fig. 1. Robust direct correlations were observed between global longitudinal strain and AHI as well as time to peak longitudinal strain and AHI. However, no such association was noted between circumferential strain parameters and AHI. There was a strong correlation between longitudinal strain of various LV segments, especially the mid and apical segments, and AHI (Fig. 2). Multiple linear regression by using a forward stepwise regression model was performed with global longitudinal strain as the dependent variable and age, body mass index, systolic blood pressure, hypertension, diabetes, LV mass index, LA volume index and AHI as independent variables (Table 4). This univariate regression showed that only AHI remained a significant predictor of global longitudinal strain in patients with severe OSA.

Based on repeated measurements of randomly selected 13 patients, ICC for inter-observer variability for global longitudinal and circumferential strains were 0.943 and 0.946 respectively. The corresponding figures for inter-observer variability were 0.847 and 0.835 (Table 5).

4. Discussion

This study sought to identify subclinical effects of severe OSA on the ventricular systolic function using speckle strain analysis by a case control methodology. Patients with very severe and symptomatic OSA were analyzed in contrast to previously published trials wherein patients with the entire spectrum of disease severity were examined. Our rationale was that this specific trial design
would amplify the differences in ventricular function between the two groups and, thus, conclusively establish whether or not OSA contributed prospectively to systolic dysfunction. Moreover, the speckle tracking technique employed in this study is a novel, sensitive and validated method for assessing myocardial systolic deformation.

The key findings of this research comprise the following: [1] the longitudinal ventricular strain was significantly reduced and time to peak longitudinal strain was notably prolonged in patients with OSA as compared to the matched population with no OSA; [2] there was no difference between the two groups with regard to circumferential strain and time to its peak; [3] alterations in longitudinal strain were more pronounced in the apical and mid
Longitudinal strain. ICC: Interclass correlation coefficient. This is attributed to the increased arterial structural alterations and hypertrophy occur in OSA independent of hypertension.\(^16\) This is explained by the hypoxic theory whereby apical segments may be more prone to ischemia than the basal segments. Due to the distal location of apical segments with respect to the coronary tree, ischemia is more likely to affect these regions in preference to more basal ones.

Another interesting finding in our analysis was that the time to peak GLS was more prolonged in apical segments compared to basal LV in patients with very severe OSA. This leads to a state where the basal segments contract earlier than the apical ones. In normal people, the time to peak longitudinal strain should be lower at apex and then increases towards the base due to the fact that electromechanical break point in LV is at the anterior septum near the apex. From there, the mechanical contraction travels back towards the base of left ventricle resulting in coordinated ejection of blood from the ventricle.\(^22\) A reversal of this pattern is seen in patients with very severe OSA, which may explain the higher heart failure symptoms in patients with severe OSA.

Our results of abnormal LV longitudinal function is in agreement with the outcomes of preceding trials which reported prolonged longitudinal systolic strain by the tissue Doppler method.\(^23\)–\(^25\).\(^11\) In a recent study using 2D speckle tracking echocardiography (STE), Haruki et al. found that the longitudinal strain was preferentially affected compared to the circumferential strain in patients with moderate to severe OSA immediately after an overnight sleep compared to pre-sleep.\(^26\) Vitarelli et al. also noted longitudinal dysfunction and increased torsion in OSA patients compared to healthy individuals, suggesting the role of myocardial ischemia as the predominant contributory factor.\(^27\) Our analysis expands these observations to find a prolongation of longitudinal strain, especially in the apical segments, without a significant alteration in circumferential strain in patients with severe OSA.

In order to ascertain the relationship between ventricular systolic dysfunction and the severity of sleep apnea, multiple linear regression analysis between AHI and strain parameters was performed. This indicated a cause-effect relation between OSA severity and longitudinal systolic strain while no such association was noted with regard to circumferential strain, thus, underpinning our finding that OSA caused predominantly longitudinal strain abnormalities.

An important clinical implication of our study may be the use of longitudinal strain of LV, especially the mid to apical involvement, for early identification of the patients with OSA at risk of ventricular dysfunction. Conversely, such a pattern of involvement can point the clinician to look for OSA as a potential cause for ventricular dysfunction. Theoretically, an early initiation of CPAP therapy in these patients can potentially avoid or even reverse the

| Variables | Global longitudinal strain | P value | Univariate regression coefficient | P value |
|-----------|---------------------------|---------|----------------------------------|---------|
| Age       | -0.116                    | 0.37    |                                  |         |
| BMI       | 0.261                     | 0.04    | 0.137                            | 0.10    |
| SBP       | 0.214                     | 0.10    |                                  |         |
| Hypertension | 0.019                  | 0.88    |                                  |         |
| Diabetes  | 0.027                     | 0.83    |                                  |         |
| LVM       | 0.118                     | 0.36    |                                  |         |
| LAVI      | 0.119                     | 0.35    |                                  |         |
| AHI       | 0.513                     | <0.01   | 0.071                            | <0.01   |

OSA: Obstructive sleep apnea, BMI: Body mass index, SBP: Systolic Blood Pressure, LVM: Left ventricular mass, LAVI: Left atrial volume index, AHI: Apnea hypopnea index.

Table 4
Independent predictors of global longitudinal strain.

Table 5
Intraobserver and interobserver variability of strain measurements expressed as interclass correlation coefficient and Chronbach’s alpha coefficient.

| Variable | ICC | 95%CI | P value | Chronbach’s Alpha |
|----------|-----|-------|---------|-------------------|
| GLS      |     |       |         |                   |
| Intraobserver variability | 0.943 | 0.826–0.982 | <0.01 | 0.971 |
| Interobserver variability | 0.847 | 0.549–0.944 | <0.01 | 0.873 |
| GCS      |     |       |         |                   |
| Intraobserver variability | 0.946 | 0.834–0.983 | <0.01 | 0.972 |
| Interobserver variability | 0.835 | 0.541–0.934 | <0.01 | 0.867 |

ICC: Interclass correlation coefficient, GLS: Global longitudinal strain, GCS: Global longitudinal strain.
adverse effects of OSA on the ventricle. Nonetheless, this hypothesis needs to be substantiated in larger controlled clinical trials.

The most important limitation of this study is the relatively small number of patients enrolled. However, the inclusion of patients with very severe disease might have amplified thecardinal manifestations of OSA and assuaged the effect of a small sample size. Another potential limitation is that the control population did not undergo a sleep study to rule out OSA; instead standard questionnaires were used, which have been proven to be very sensitive in making the diagnosis. Thirdly, we had to exclude six patients in the OSA group and two in the control group due to inadequate image quality which could theoretically confound the results. However, despite excluding these patients, both the groups are well matched for potential confounders. Next, the patients with hypertension were not excluded: this could, theoretically, confound the results arrived at. Nonetheless, as both groups were well matched for the occurrence of hypertension as well as systolic blood pressure, this bias might have been largely negated. Finally, LV hypertrophy was significantly more in the OSA group than in the control group, a finding described in prior studies of OSA patients. It is difficult to exclude higher LV mass, rather than OSA per se, as the cause of the abnormal longitudinal strain by our study. However, the fact that mid-apical dominant longitudinal strain pattern has not been previously described in other causes of LVH favours OSA as the etiology behind these findings.

5. Conclusion

Using speckle tracking echocardiographic techniques, this investigation revealed that symptomatic, very severe OSA is associated with longitudinal ventricular systolic dysfunction, which is predominant at the apical segments of the left ventricle. This is probably owing to frequent and recurrent hypoxia occurring during sleep in these patients. Large clinical studies are required to define whether this subclinical ventricular systolic dysfunction has clinically relevant consequences and also whether treatment options such as continuous positive airway pressure therapy would facilitate reversing these effects on the ventricle.

Author contributions

MJV, G Sharma, G Shukla, SS and SM were involved in concept and design of the study, data analysis and manuscript preparation. AG was involved in patient recruitment and data analysis. VKB was involved in critical revision and approval of article.

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