Evaluation of subclinical left ventricular systolic dysfunction in patients with obstructive sleep apnea by automated function imaging method; an observational study

Obstrüktif uyku apneli hastalarda subklinik sol ventrikül sistolik disfonksiyonunun otomatik fonksiyonel görüntüleme yöntemiyle değerlendirilmesi: Gözlemsel bir çalışma

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ABSTRACT

Objective: We aimed to evaluate the subclinical left ventricular (LV) systolic dysfunction with the automated function imaging method (AFI) based on speckle tracking echocardiography (STE) in obstructive sleep apnea patients (OSA) with normal left ventricular ejection fraction (LVEF) and without any confounding disease that can cause myocardial dysfunction.

Methods: Twenty-one healthy individuals and 58 OSA patients were included in this observational cross-sectional study. According to the severity of disease, OSA patients were examined in three groups; mild, moderate and severe OSA. Apical 2-, 3- and 4- chamber images were obtained for AFI evaluation. The global systolic longitudinal strain (GL_S) values were determined for each view, and averages of these were used in comparison of the patient groups. One-way ANOVA, Kruskal-Wallis, Pearson correlation tests and linear regression analysis were used for statistical analysis.

Results: The GL_S values of the OSA patients were lower than of the healthy individuals and these values were decreased along with the OSA severity (Healthy:-25.58±-2.16%, Mild:-23.93±-3.96%, Moderate:-21.27±-2.60%, Severe:-16.94±-2.66%, respectively). The difference was significant between moderate OSA patients and healthy individuals, and significant between severe OSA patients and all other groups ($p<0.03$). The apnea-hypopnea index was found to be correlated with the GL_S (β=-0.659, 95% CI: 0.09-0.17, $p<0.001$).

Conclusion: Longitudinal LV mechanics in OSA patients with normal LVEF are deteriorated in the subclinical stage being associated with the severity of disease. AFI can be used as an effective and safe method in the determination of subclinical myocardial dysfunction in OSA patients, because it is semi-automated and easy to use with a short analysis time.

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Key words: Obstructive sleep apnea, speckle tracking echocardiography, myocardial strain, regression analysis

ÖZET

Amaç: Sol ventrikül ejeksiyon fraksiyonu normal ve miyokart fonksiyonlarını etkileyecek ek hastalığı bulunmayan, obstrüktif uyku apneli (OUA) hastalarda, subklinik sol ventrikül sistolik disfonksiyonunu, iki boyutlu benek izleme ekokardiyografi tekniğine dayanan, otomatik fonksiyonel görüntüleme yöntemi (OFG) ile değerlendirmeyi amaçladık.

Yöntemler: Gözlemsel enine-kesitli çalışmamıza 21'i sağlıklı, 58'i OUA hastası olan toplam 79 kişi alındı. OUA'lı hastalar hastalığın ciddiyetine göre hafif, orta ve ağır olarak 3 gruba ayrıldı. OFG değerlendirmesi için sol ventrikülün apikal 2-, 3-, 4- boşluk görüntüleri kullanıldı. İlgili boşluklara ait sistolik longitüdinal deformasyon değerlerinin aritmetik ortalaması olan, global longitüdinal deformasyon değerleri gruplar arasında karşılaştırıldı. İstatistiksel analiz için tek -yönlü ANOVA, Kruskal-Wallis, Pearson korelasyon testleri ve doğrusal regresyon analizi kullanıldı.

Bulgular: Sağlıklı gruba göre hafif OUA grubundan itibaren hastalığın ciddiyeti ile global longitüdinal deformasyon değerleri azalmaktaydı (Sağlıklı: -%25.58±-2.16, Hafif OUA: -%23.93±-3.96, Orta OUA: -%21.27±-2.60, Ciddi OUA: -%16.94±-2.66). Orta OUA grubundan itibaren gruplar arası fark anlamlıydı ($p<0.03$). Ağır OUA grubunun değerleri tüm gruplardan düşük bulundu. Global longitüdinal deformasyon değerleri apne hipopne indeksi (AHİ) ile ilişkili bulundu (beta=-0.659, 95% GA: 0.09-0.17, $p<0.001$).

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Sonuç: Sol ventrikül ejeksiyon fraksiyonu normal OUA'lı hastalarda miyokardın longitüdinal fonksiyonları hastalığın ciddiyetine bağlı olarak subklinik evrede bozulabilir. AFI yöntemi yarı otomatik olması ve kullanım kolaylığının yanısıra kısa analiz süresi sayesinde, OUA'lı hastalarda miyokart fonksiyonlarının değerlendirilmesinde mevcut ekokardiyografik yöntemlere ek olarak, etkili ve güvenilir bir yöntem olarak kullanılabilir. *(Anadolu Kardiyol Derg 2012; 12: 320-30)*

Anahtar kelimeler: Obstrüktif uyku apne, benek izleme ekokardiyografi, miyokardiyal deformasyon, regresyon analizi

Introduction

Obstructive sleep apnea (OSA) is a syndrome characterized by repeated episodes of upper respiratory tract obstruction episodes during sleep and commonly a decrease in arterial oxygen saturation. Cardiovascular disturbances are the most serious complications of OSA (1). Several clinical and echocardiographic studies consistently showed that OSA might contribute to the disturbance of myocardial structure and functions.

Determination of myocardial function is vital for the clinical evaluation of cardiovascular disease. Echocardiography is the most common imaging modality used today to assess left ventricular (LV) myocardial function; the most widely used clinical tool to quantify LV systolic function is the ejection fraction (EF), however, it has some technical limitations. Assessment of EF by visual assessment is operator dependent with significant inter and intraobserver variability, and interpretation of regional myocardial function usually is subjective to semi-quantitative visual assessment of wall thickening and endocardial excursion (2, 3). The detection of LVEF, which is an index reflecting endocardial displacement may not be suitable for the assessment of systolic function in hearts with concentric remodeling/ hypertrophy such as those of patients with OSA, hypertension (4, 5). The LV chamber function depends in part on LV geometry. A concentric geometry may contribute to detection of a normal ejection fraction despite impaired mid-wall myocardial shortening and myocardial longitudinal function (6, 7).

Strain imaging measures the magnitude of regional active myocardial deformations. This technique enables the differentiation and passive motion due to tethering. It can be measured utilizing either tissue Doppler imaging (TDI) and more recently by two-dimensional (2D) echocardiographic speckle tracking (2D-STE) derived parameters. 2D-STE is a new echocardiographic tool for obtaining strain and strain rate measurements by tracking speckles in the ultrasonographic image in two dimensions. STE is easy to perform, and it requires only one cardiac cycle to be acquired; further interpretation can be done after image acquisition. The 2D-STE method is not based on tissue Doppler measurements, consequently it is not angle dependent (8, 9). Automated function imaging (AFI) was recently introduced which reflect systolic LV function, based on 2D-STE imaging by assessment of global LV longitudinal strain (L_S). This imaging technique discriminates between active and passive myocardial motion and enables the angle-independent quantification of myocardial deformation in two dimensions (10).

No studies were found in the literature, which examined subtle left ventricular dysfunction with the speckle tracking echocardiography based AFI method.

We aimed to investigate the relationship between the presence of OSA and severity, and subclinical systolic dysfunction, by comparing LV peak L_S values detected by AFI method in OSA patients, who had normal LVEF, and had not have pulmonary hypertension or any other concomitant diseases affecting the myocardial functions, with the values in healthy individuals.

Methods

Study design

This study was designed as an observational cross-sectional study.

Study population

Patients between ages 30 and 60 years with OSA diagnosis who were examined in the Akdeniz University Faculty of Medicine, Department of Chest Diseases outpatient clinic between dates March 2009 and October 2010 were included in this study after conducting polysomnographies at the sleep laboratory. As a control group, we chose asymptomatic healthy individuals aging between 30 and 60 years without cardiovascular diseases who visited Akdeniz University Department of Cardiology outpatient clinic for cardiovascular check-up. The healthy group used in the study included patients suitable for the study from the perspective of cardiac anatomy and functions, those with no night snoring or day-time sleepiness, who scored less than 10 in the Epworth sleepiness scale, and had low risk of OSA in the Berlin survey form evaluation (11, 12). Echocardiographic evaluation was performed in Akdeniz University Department of Cardiology.

Exclusion criteria were as follows: angina and angina equivalent symptoms, abnormal electrocardiography, abnormal cardiovascular stress test and abnormal myocardial scintigraphy, an LVEF lower than 50%, mean pulmonary artery pressure (MPAP)>25 mmHg, individuals with structural heart disease and rhythm problems, a documented history of coronary and peripheral vascular diseases, diabetes mellitus, body mass index (BMI)>35 kg/m^2, hypertension(in the physical examination, patients with a systolic blood pressure value of >140 mmHg and diastolic blood pressure value of >90 mmHg after averaging three separate blood pressure measurements taken at 10 minute intervals, as well as, patients receiving antihypertensive treatment were accepted as hypertensive), restrictive and obstructive pulmonary disease, individuals who have systemic and metabolic diseases that could adversely affect the cardiac structure and functions, and smoking. Also, patients who were receiving OSA treatment were excluded.

Informed consent was obtained from every individual included in the study, and the local Ethical Committee of Akdeniz University Medical School approved the study.

All individuals blood pressures, pulses, anthropometric measures were recorded before echocardiography. Body mass index (BMI) and body surface areas (BSA) were derived from the anthropometric measures.

Polysomnography

Polysomnography was performed with 16 channels Embla (Medcare Inc. Iceland) with continuous monitoring from a sleep technician. The system consists of 4 channels of electroencephalography, 2 channels of electrooculography, submental electromyography, oronasal airflow, thoracic and abdominal movements, pulse oximeter oxygen saturation, tibial EMG, body position detector, electrocardiogram and tracheal sound. Sleep stages were scored according to the standard criteria of the American Academy of Sleep Medicine (13). Apnea was defined as complete stopping of airflow lasting more than 10 seconds. Hypopnea was defined as 30% or more reduction in respiratory airflow lasting more than 10 seconds which is accompanied by a decrease of >4% in oxygen saturation. The average number of episodes of apnea and hypopnea per hour of sleep was defined as the apnea hypopnea index (AHI). According to the severity, included patients were classified as mild OSA (AHI between 5 and 15), moderate OSA (AHI between 15 and 30) and severe OSA (AHI>30) (14).

Echocardiographic measurements

Echocardiography was performed in left lateral decubitus position with an ultrasound machine GE-Vingmed Vivid 7 system (GE-Vingmed Ultrasound AS, Horten, Norway) and 3S-RS (3.5 MHz) probe. Averages of three consecutive cycles were measured for all echocardiographic data. Images were obtained from parasternal and apical position using 2D, M-Mode and Doppler echocardiographic techniques. Examinations were performed by two experienced cardiologists who were unaware of the groups of individuals. The LV end diastolic and end systolic dimensions, interventricular septum and posterior wall thickness measures were obtained from M-mode echocardiography. LV mass calculated according to the anatomically validated Devereux formula (15). LV mass index (LVMI) was calculated by dividing LV mass by the body surface area. Relative wall thickness (RWT) was calculated according to the following formula: 2 (end-diastolic posterior wall thickness) / (left ventricle end-diastolic dimension) (4). LVEF was measured using biplane Simpson's method, left atrial volume (LAV) was determined by the biplane area length method from apical four and two chambers views according to recommendation of American Society of Echocardiography (16). LAV indexes (LAVI) were calculated by dividing of the LAV to the BSA. Pulse wave Doppler 3 mm sample volume was taken from proximal to the mitral valve tips in the apical four chamber view to record LV inflow velocity and early diastolic peak flow velocity (E), late diastolic peak flow velocity (A) and deceleration time of the E wave velocity (DecT) were measured. Isovolumetric relaxation times (IVRT) were also calculated from LV inflow and outflow tract velocities. E/A ratio was calculated (17).

The mean pulmonary artery pressure (MPAP) was calculated with the Mahan Formula [90-(0.62*right ventricle acceleration time)], and the systolic PA pressure (SPAP) was estimated from the sum of the peak right atrium-right ventricle gradient and estimated right atrial pressure (18).

Tissue Doppler imaging (TDI) was recorded from the apical four-chamber view with the pulse-wave Doppler sample volume placed on the septal and lateral mitral annulus of the LV. The all of the annular velocities and time intervals of tissue Doppler analysis were calculated as an average of the two annular sites of the LV. Peak systolic (S) velocity and peak early (E') were measured. The ratios between E/E' were calculated (19). Averages of three consecutive cycles were measured for all echocardiographic data.

Automated functional imaging techniques

For the assessment of LV longitudinal strain (L_S), dedicated automated function imaging (AFI) protocol was used. Two-dimensional grayscale images were acquired in the standard 3 apical views (apical 3-chamber, apical 4-chamber and apical 2-chamber) at a frame rate of 70-90 frames/sec and 3 cardiac cycles were recorded. The images were analyzed with Automated Function Imaging method by using a software package Echopac PC (Version 8.0. GE Healthcare, Horten, Norway). The end systolic frame is defined in the apical long axis view. The closure of the aortic valve is marked, and the software measures the time interval between R wave and aortic valve closure. This interval is used as a reference for the echocardiographic view loops. The detection of tracked area was carried out semi-automatically after selection two basal corners at the level of mitral annulus and third point in the apex, with optional manual correction. In each of the apical views, LV walls were divided into six segments, for each LV segment the value of strain and quality of tracking were then assessed. The mean L_S value was calculated for each of the three views (20). The value of the global longitudinal LV strain (GL_S) was calculated as the arithmetical mean of the values. In addition to this, basal, mid and apical strain values for each image window were detected, and after the arithmetical mean of related values was calculated, GL_S values for basal, mid and apical segments were compared between the groups. In general, L_S values are presented as negative values; a larger negative value indicates a larger extent of L_S.

Statistical analysis

SPSS 18.0 statistical analysis software (SPSS Inc, Chicago, IL, USA) was used to evaluate variables and test. Numeric variables are presented as mean±standard derivation or median

(minimum-maximum) values and categorical variables as rates. Three or more group comparisons were performed by one-way ANOVA test for normally distributed variables. Kruskal- Wallis test was used for comparison of ordinal variables or continuous variables, which were not normally distributed among groups. Tukey test was used for post-hoc analysis after performing ANOVA test. Mann-Whitney U test with Bonferroni correction was used for post-test analysis after performing Kruskal Wallis test. Alpha (α) critical value for Mann-Whitney U test in Bonferroni correction was accepted as 0.03 because the Mann-Whitney U test result below 0.03 is insignificant. The normality analysis was performed by Kolmogorov-Smirnov test. The relationships between the LV GL_S parameter and AHI, LV echocardiographic parameters and the clinical and demographic data of the individuals who were included in the study were analyzed using Pearson's correlation test. After the analysis, the model formed with parameters found to be statistically significant were evaluated with linear regression analysis and the relative relationship of each parameter with LV GL_S values was separately assessed. All the hypotheses were constructed as two tailed and an alpha critical value of 0.05 was accepted as significant.

Inter-and intra-observer variability

Intra-observer variability was determined by the observer repeating the measurement of the peak GL_S ST in 20 random OSA patients or control subjects 2 weeks after the first measurement. Inter-observer variability was determined by another observer measurement of those variables in the same database. Intra- and inter-observer variability`s were then calculated as the absolute difference between the corresponding two measurements as a percent of their mean. Intra- and inter-observer reproducibility`s were evaluated by means of the intra-class correlation coefficient (ICC).

Results

Demographic and clinical results

A total of 79 individuals enrolled into our study; 21 were healthy individuals and 58 were OSA patients. Patients with OSA were divided into 3 groups according to their apnea-hypopnea indexes: mild OSA = 20, moderate OSA =19 and severe OSA=19. Clinical and demographic data other than BMI were not different among groups; BMI was greater in the severe OSA group than that of healthy group (29.80±2.38 vs 26.35±4.14 kg/m^2; p=0.006). AHI values of OSA groups were increased in line with the disease severity (p<0.001). The demographic, clinical data and AHI values of the groups are presented in Table 1.

Echocardiographic results

The M-mode, 2D, pulse wave Doppler and tissue Doppler echocardiographic variables are presented in Table 2. Although interventricular septum and posterior wall thicknesses, and the RWT in the OSA groups were greater than the healthy individuals (p<0.001), these parameters were not different among OSA groups. While LVMI from the healthy group was increased with severity of the disease, there was a significant difference between the severe OSA and healthy control groups (p=0.004). While the E/A ratio in mild OSA group were lower than that of healthy controls (p=0.009), there was no difference between the other groups. LAVI, DecT and IVRT values were increased with the disease severity, and the significant differences were observed between groups starting from the mild OSA patients (p<0.001). The EF and fractional shorting values were not different among groups, TDI-S velocities were not different among groups (p>0.05). While the E/E' ratio was increased in line with the disease severity, there was a significant difference especially between severe OSA group and the other groups (p<0.001).

Table 1. Clinical, demographic characteristics and AHI values of the patients and healthy individuals

Variables	Healthy (n=21)	Mild OSA (n=20)	Moderate OSA (n=19)	Severe OSA (n=19)	*Chi-square /F	*p
Age, years	45.4±4.6	46.9±6.5	46.79±5.1	46.7±7.7	1.37	0.257
Female, n (%)	11 (52.4)	5 (25)	5 (26.3)	3 (15.8)	7.1	0.068
BMI, kg/m^2	26.3±4.2	28.7±3.4	29.1±2.3	29.8±2.4†	4.42	0.006
SBP, mmHg	120.9±10.6	118.8±6.1	120.2±6.8	121.1±8.1		0.839
	120 (100-140)	120 (110-130)	120 (110-130)	120 (110-140)	0.85	
DBP, mmHg	75.5±6.7	76±6.19	73.68±5.97	75.79±5.07		0.577
	80 (60-90)	80 (60-80)	70 (60-80)	80 (70-80)	1.98	
Pulse, beats/min	74.3±10.9	76±7.1	77.2±5.5	78.2±6.2		0.283
	72 (55-100)	78 (57-90)	78 (62-87)	77 (65-89)	3.8	
AHI, per hour	N/A	10.7±2.6	20.5±2.6‡	58.1±16.2‡,**	132.2	<0.001

Data are presented as number (percentage), mean±standard deviation and median (minimum-maximum) values

*Kruskal Wallis test and one-way ANOVA test

Post-hoc Tukey test and post-test Mann-Whitney U test with Bonferroni correction: †-p<0.03 compared with healthy, ‡-p<0.03 compared with mild OSA, **- p<0.03 compared with moderate OSA

AHI- apnea hypopnea index, BMI-body mass index, DBP-diastolic blood pressure, N/A-non-appropriate, OSA – obstructive sleep apnea, SBP-systolic blood pressure

Table 2. Left ventricular 2D, Doppler and tissue Doppler echocardiographic parameters of the patients and the control group

Variables	Healthy (n=21)	Mild OSA (n=20)	Moderate OSA (n=19)	Severe OSA (n=19)	*Chi-square /F	*p
EF, %	64.2±3.7	64.2±3.8	63.7±5.4	63.2±3.2	1.27	0.736
FS, %	35.6±2.4	35.1±3.3	35.8±2.6	37.5±5.2		0.242
	35 (32-42)	34 (32-45)	35 (32-43)	35 (30-48)	4.19	
IVSD, cm	0.89±0.09	1.03±0.1†	1.03±0.13†	1.13±0.13†		<0.001
	0.9 (0.7-1)	1 (0.8-1.2)	1 (0.9-1.3)	1.1 (0.9-1.4)	28.41	
PWD, cm	0.88±0.07	1.03±0.09†	1.04±0.12†	1.11±0.13†		<0.001
	0.9 (0.8-1)	1 (0.9-1.2)	1 (0.9-1.2)	1.1 (0.9-1.3)	29.93	
LVMI, g/m²	86.5±18.7	93.2±16.6	94.5±22.9	103.5±22.9†	2.35	0.004
RWT	0.38±0.05	0.47±0.06	0.47±0.06	0.5±0.08†	13.27	<0.001
Mit E/A	1.19±0.24	0.96±0.16†	1.01±0.3	1.11±0.28		0.009
	1.18 (0.87-1.8)	0.93 (0.77-1.24)	1.03 (0.6-1.51)	1.05 (0.71-1.7)	11.62	
DecT, msec	163±26.2	227.4±31.1†	216.4±60.4†	199.4±39.5†		<0.001
	170 (108-209)	230 (161-274)	226 (169-284)	188 (129-292)	31.47	
IVRT, msec	88.3±12.5	106.3±12.8†	108.8±12.9†	113.2±10.4†	16.43	<0.001
S (cm/sec)	10.2±1.94	9.7±1.16	9.5±1.94	9.16±1.56	1.27	0.290
E/E'	6.88±1.7	6.91±1.9	8.56±2.37	10.29±1.48†,‡,**	30.3	<0.001
	6.65 (4.75-10.23)	6.33 (4.19-13.2)	7.58 (5.9-14.03)	10.37 (7.37-12.94)		
LAVI, ml/m²	21.6±4.7	22.2±4.8	27.44±6.9†	32.3±5.1†,‡	16.8	<0.001
S-PAP, mmHg	25.6±5.4	27.6±4.3	29.8±4.2	32.1±3.7	1.67	0.180
M-PAP, mmHg	19.9±2.8	18.1±5.4	17.7±4.7	18.7±4.4	1.96	0.417

Data are presented as mean±standard deviation and median (minimum-maximum) values
*Kruskal Wallis test and one-way ANOVA test
Post-hoc Tukey test and post-test Mann-Whitney U test with Bonferroni correction: † - p<0.03 compared with healthy, ‡ - p<0.03 compared with mild OSA,** - p<0.03 compared with moderate OSA
DecT - deceleration time, E/A - ratio between early and late diastolic inflow velocities, E/E '- ratio between early diastolic inflow velocity and early diastolic annular myocardial velocity EF - ejection fraction, FS - fractional shortening, IVRT - isovolumic relaxation time, IVSD - interventricular septum diastolic thickness diameter, LAVI - left atrial volume index, LVMI - left ventricular mass index, M-PAP - mean pulmonary artery pressure, PWD - posterior wall diastolic thickness diameter, RWT - relative wall thickness, S - systolic annular myocardial velocity, S-PAP - systolic pulmonary artery pressure

Automated functional imaging results

The LV-L_S values determined by AFI method are presented in Table 3. In addition to the L_S values of LV images obtained from apical 3-, 4-, and 2 -chamber views, the GL_S parameter, which was calculated by using the related values, were decreased with the disease severity starting from the moderate OSA patients. Especially the severe OSA patients have lower GL_S values than those of other groups (p<0.001). Besides the GL_S evaluation, in our study we performed regional analysis in terms of basal, mid and apical segmental L_S parameters. In all groups, L_S values were increasing from basal to apical segments. Similar to the GL_S, segmental strain parameters were in decreasing trend along with the disease severity, and the difference was statistically significant in comparison of moderate OSA patients with healthy individuals and in comparison of severe OSA patients with all other groups (p<0.001). LV longitudinal strain parameters in healthy individuals (A) and OSA patients (B) are presented in Figure 1.

Relationship between echocardiographic variables and AHI

In the correlation analysis, GL_S was found to be correlated with BMI, LVMI, IVRT, E/E', LAVI, RWT and AHI parameters, however, linear correlation analysis results indicated that only the AHI parameter has a contribution to the model which describes the GL_S variable (β=-0.659, 95% CI: 0.09-0.17, p<0.001/). The results of correlation and regression analysis results are presented in Table 4.

Inter-and intra-observer variability`s

Twenty patients were randomly selected for the assessment of intra and interobserver variability in measurements of GL_S. The intra- and inter-observer reproducibility of GL_S parameter

Table 3. Left ventricular longutidinal systolic strain values of the patients and the control group

Variables	Healthy (n=21)	Mild OSA (n=20)	Moderate OSA (n=19)	Severe OSA (n=19)	*F	*p
L_S-4C, %	-26.6±-2.4	-24.6±8.6	-21.3±-3.5†,‡	-15.3±-2.9†,‡,**	19.07	<0.001
L_S-3C, %	-24.5±-2.5	-22.6±-2.6	-20.4±-3.2†	-17.1 ±-3.5†,‡,**	22.38	<0.001
L_S-2C, %	-25.7±-2.9	-24.6±3.2	-22.1±-3.8†	-18.4 ±-3.6†,‡,**	18.17	<0.001
GLS, %	-25.6±-2.2	-23.9±-3.9	-21.3±-2.6†,‡	-16.9 ±-2.7†,‡,**	32.74	<0.001
L_S-B, %	-21.4±-1.9	-19.9±-2.4	-18.4±-2.6†	-15.3±-2.9†,‡,**	21.05	<0.001
L_S-M, %	-23.3±-2.1	-21.5±-2.4	-19.7±-2.6†	-16.9±-2.9†,‡,**	23.07	<0.001
L_S-A, %	-27.4±-3.7	-24.6±-2.9	-23.5±-3.9†	-19.2±-3.9†,‡,**	17.1	<0.001

Data are presented as mean±standard deviation values
*one-way ANOVA test
Post-hoc Tukey test: † - p<0.03 compared with healthy, ‡ - p<0.03 compared with mild OSA,** - p<0.03 compared with moderate OSA
GL_S- global longitudinal systolic strain, L_S B- M- A- longitudinal systolic strain basal, mid, apical segments, L_S 4C- 3C- 2C- longitudinal systolic strain calculated from apical 4- 3- 2 chamber views, OSA- obstructive sleep apnea

was shown acceptable. The intra- and inter-observer variations were 4.1% and 5.2% for GL_S. Corresponding ICC was 0.95.

Discussion

Our study results indicated that, especially beginning with the moderate OSA patients, the longitudinal LV functions decrease along with the disease severity in OSA patients despite the LVEF is not different among OSA patients and healthy individuals. The decrease in longitudinal LV functions was found to be correlated with the presence and severity of OSA. The LVH and diastolic dysfunction were found to accompany the decrease in longitudinal LV functions in OSA patients.

Various factors have been accused for negative effects of OSA on myocardial structure and functions. Especially hypoxia and hypercapnia, which ensues during sleeping; increased negative intrathoracic pressure during the arousal phase and hemodynamic changes, which occur during sympathetic system activation; oxidative stress, systemic inflammation, endothelial dysfunction, oxygen demand of myocardium and imbalances during presentation may cause myocardial damage. Apoptosis develops due to chronic myocardial cellular damage, and cardiac dysfunction develops due to myocardial fibrosis. Besides the direct effects of OSA on myocardial structure and functions, concomitant pathologies like hypertension, diabetes, obesity, and coronary artery diseases also assist in the development of myocardial dysfunction (21, 22).

Left ventricular hypertrophy regardless of the underlying cause was found to be associated with increased cardiovascular morbidity and mortality. Patients with OSA have coexisting disorders, which have been associated with LVH such as obesity, hypertension and diabetes mellitus (23, 24). In our study, despite the exclusion of patients with hypertension, diabetes mellitus and despite the BMI is not different among groups except for the severe OSA patients, the septal, posterior wall thicknesses, RWT and the LVMI were found to be greater in OSA patients than the healthy individuals. These results support the previous studies, which indicated that the OSA might cause LVH independent of hypertension, diabetes and obesity (25, 26).

The increase in afterload in OSA is the most encountered factor in development of the LVH. The increase in LV afterload in OSA can be explained with the following reasons; increased negative intrathoracic pressure, associated with attempted breathing against an occluded upper airway and increased systemic blood pressure associated with increased sympathetic nervous system activity, hypoxemia and arousal from sleep. Forced inspiration against increased airway resistance during wake fullness raises aortic transmural pressure, and it leads to aortic stiffness and LV systolic load increase (14, 21, 22, 27)

LV diastolic dysfunction has been suggested to be a common finding in OSA patients. In addition, the diastolic dysfunction is a significant risk factor for development of systolic dysfunction (28, 29). In our study, the greater LAVI, IVRT and DecT values indicate the relationship between the OSA and diastolic dysfunction. In addition to these findings, the E/E' ratio was increased along with the OSA severity. Especially the relationship between the E/E' ratio and the increased left ventricle filling pressures have demonstrated that filling pressures have been increased with the severity of OSA and increased concomitant diastolic dysfunction. Besides, the relationship between the increased E/E' ratio and myocardial fibrosis indicated that myocardial dysfunction and myocardial fibrosis might be increased in OSA patients in relation to the OSA severity (30). The relationship between GL_S value and E/E' indicated that increased left ventricle filling pressures and endocardial fibrosis might be the influential factors in development of the subclinical LV systolic dysfunction.

LV systolic function is a complex coordinated action that involves longitudinal contraction resulting with the shortening and twisting movement in the longitudinal axis, and circumfer-

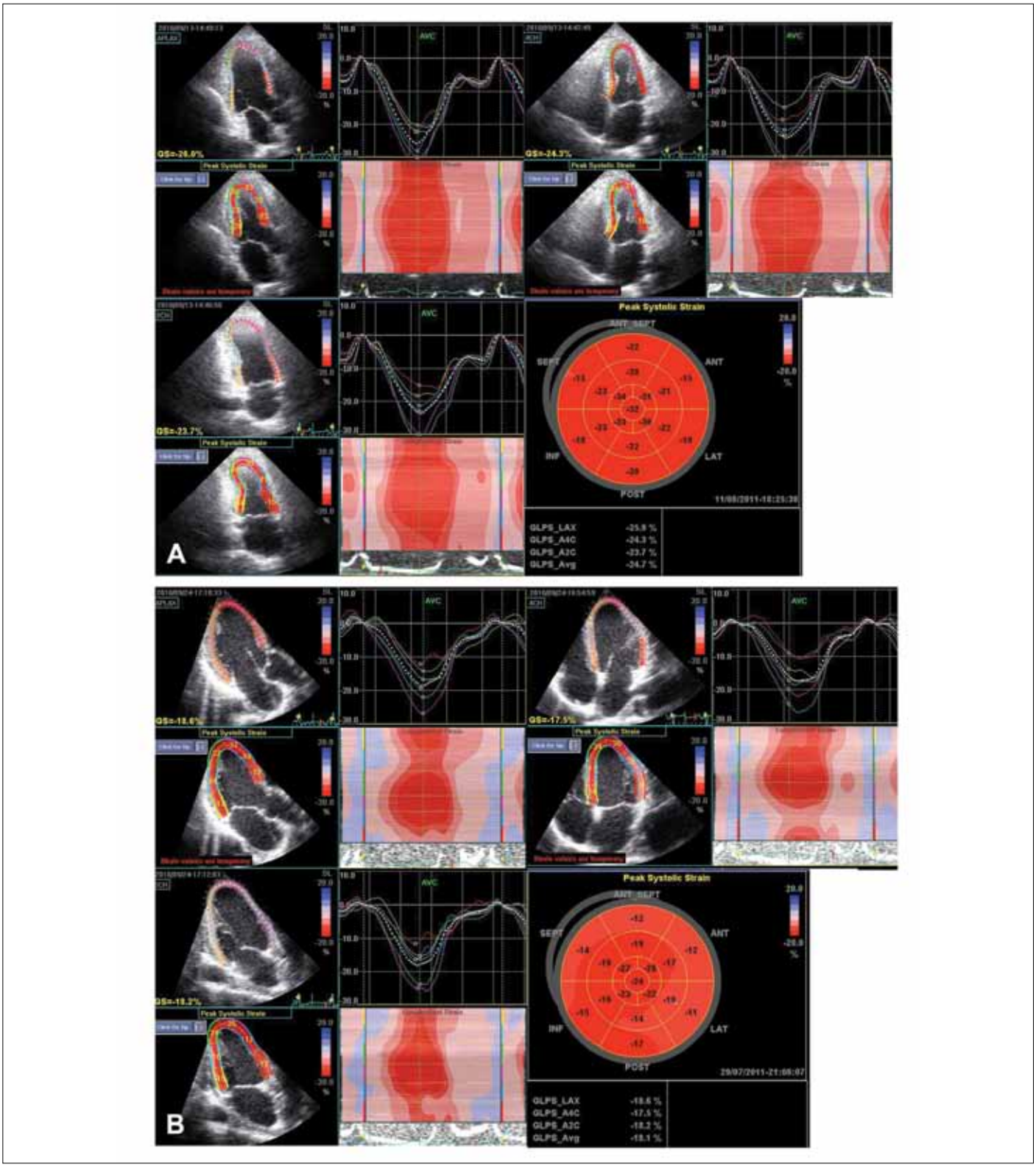

Figure 1. Example of speckle tracking strain imaging used automated functional imaging. After the LV endocardial border is manually delineated, a 6- segment model is created, and speckle tracking LV longitudinal strain curves are automatically generated. After apical 3-, 4- and 2- chamber analysis, the longitudinal strain values of the segments are given in the "bull's eye report" which is formed by the software. At the bottom of graphic, a detailed report of apical 3-, 4- and 2- chamber view and left ventricular global ventricular strain values is seen. Comparative display of left ventricular longitudinal strain parameters in healthy individuals (A) and OSA patients (B). When compared with healthy individuals, OSA patients have lower segmental and global longitudinal strain values

LV - left ventricle, OSA - obstructive sleep apnea

Table 4. Linear regression analysis of the relationship between left ventricular longutidinal strain and clinical and echocardiographic variables

Variables	Beta	95% Confidence interval		p
		Lower bound	Upper bound	
BMI	-0.12	-0.08	0.39	0.2
LVMI	-0.04	-0.03	0.04	0.7
IVRT	-0.22	0.002	0.12	0.06
E/E'	-0.05	-0.49	0.3	0.26
LAVI	-0.06	-0.18	0.1	0.58
RWT	-0.14	-4.29	20.49	0.55
AHI	-0.66	0.09	0.17	<0.001

AHI - apnea hypopnea index, BMI - body mass index, E/E' - ratio between early diastolic inflow velocity and early diastolic annular myocardial velocity, IVRT - isovolumic relaxation time, LAVI - left atrial volume index, LVMI - left ventricle mass index, RWT - relative wall thickness

ential and radial contraction resulting with the shortening and thickening in the horizontal axis. The longitudinal LV mechanics, which are primarily governed by the subendocardial region, are the most vulnerable component of LV mechanics, therefore, it is the most sensitive part in a myocardial disease (31). The LVH and diastolic dysfunction which accompany OSA disease may lead to subendocardial dysfunction. This dysfunction is most likely caused by fibrosis related to the increased wall stress and microvascular disturbances. Repetitive hypoxia due to sleep -induced apnea may adversely affect the interaction between myocardial oxygen demand and supply resulting in the development of subendocardial ischemia and subclinical LV systolic dysfunction (32). Subendocardial dysfunction subsequently complicates the longutidinal contractile function. Interestingly, the reduction in longutidinal function is initially compensated by radial and circumferential function aggravation because of the cross-fiber shorting phenomenon (33).

In the present study, although the TDI-S was not significantly different among OSA patients and healthy individuals, the S value was found to be decreased along with the disease severity. LV systolic longutidinal dysfunctions of myocardium can be evaluated quantitatively by TDI method. Previous TDI studies have showed that OSA accompanied by sleep-induced LV systolic longutidinal dysfunction (34-36). TDI is more sensitive than EF in the detection of subtle changes in the LV contractile function. However, TDI values depend mainly on the insonation angle of the ultrasound beam and thus cannot be obtained for all LV segments. In addition, tethering and translation, preload and afterload changes influence velocity data (37). Furthermore, high frame rate imaging, ideally >130 frames per second, is required for this method.

In our study, we investigated the correlation between OSA and subclinical systolic dysfunction by comparing GL_S values of OSA patients with normal LVEF and those of the healthy controls. While GL_S values started to decrease from the moderate OSA group with the disease severity compared to healthy controls, the values especially in the severe OSA group were lower than those in the healthy controls, as well as the mild and moderate OSA patients groups. In addition to GL_S value, strain values of basal, mid and apical segments were also compared between the groups. In general, strain values were observed to increase from basal segments to apex in all groups. When strain values in basal, mid and apical segments were compared between the groups, strain values in all segments were decreased with the disease severity starting from the moderate OSA group, whereas values of the severe OSA group were lower than those in all groups. Differences between the groups were more prominent in the apical segments than the other segments. In addition to correlation, which was observed between GL_S value determined by AFI and AHI, the high consistencies of intraobserver and interobserver GL_S values have supported that AFI method may be an efficient and reliable method in detecting subclinical myocardial dysfunction.

There are only two published studies that have used STE in the assessment of longitudinal, circumferential and radial systolic myocardial functions in OSA patients. In the study of Haruki et al. (38), STE was used in OSA patients before and after sleep to determine the acute effect of OSA on cardiac functions by comparing S values in all three directions. While the myocardial S values in all three planes decreased in the after-sleep period, the difference was only found to be significant between longitudinal fibers (38). Vitarelli et al. (39) found in their study that longitudinal myocardial functions decrease in OSA patients compared to healthy individuals, even the LVEF of both groups were not different. Even the longitudinal functions were decreased; the LV torsion increased significantly in OSA patients compared to healthy individuals, as a result of a predominant increase in apical rotation, and this was independently related to AHI and aortic stiffness. The changes of LV have been shown to be independent of the accompanying diastolic dysfunction, LVH and co-morbid diseases (39). The conclusion of the researches have illustrated that apnea-hypopnea periods that develop during sleep especially affect subendocardial-located longitudinal fibers; this conclusion also supports the theory that longitudinal fibers are affected in the early stages of OSA.

Speckle tracking, a novel method based on pure, two dimensional gray scale ultrasound acquisitions, has recently been implemented to calculate global and regional strain. Compared to other TDI, regional strain has the advantages of independence from translation and tethering. A great advantage of this method is that it is angle independent and can provide information on deformation in more than one direction. Besides these technical advantages, the inter- and intraobserver reproducibility is generally better with 2D-STE method (40).

The AFI algorithm is a novel method based on 2- dimensional strain imaging that enables quantification of myocardial strain simultaneously in different LV segments with ultrasound beam angle independency by tracking acoustic pixels equally distributed within the myocardial wall. As applied to apical views, this method allows for the measurement of regional myocardial shortening and subsequently enables the calculation of global LV strain as the average of the 18 -segment longitudinal peak systolic values (41). Two-dimensional global longitudinal strain obtained with the AFI technology provides objective and quantitative assessments of LV function. AFI is novel, angle independent, more reproducible, apparently simpler, and computationally faster speckle tracking technique (20). In various studies, which were conducted on patients with systolic heart failure and AFI method was used, GL_S value defined by AFI was correlated with the wall motion score determined by angiography and echocardiography. In another study, GL_S values, which were evaluated by AFI in patients with heart failure with normal LV ejection fraction, were lower than those in the healthy controls (42, 43). Small variations between intraobserver and interobserver measurements in the related studies have demonstrated that the related method was reliable in evaluating the left ventricle functions.

Study limitations

One limitation of our study is that we have used Epworth and Berlin scale method rather than the AHI for selection of controls. However, in daily clinical practice, we use those methods to select appropriate patients for the polysomnography test. In the present study, hypertensive patients were excluded from our study, however we were not able to assess the effects of possible increased blood pressure during sleeping which could be induced by apnea and hypopnea episodes. In our study, BMI was higher especially in the severe OSA group than the healthy group, so it might be effective in the RV and LV functions. However, correlation between the parameters continued even after BMI adjustment suggested that BMI had effects on results of the study. Because of the technical limitations of AFI method, the circumferential and radial LV functions could not be assessed in our study. Although the efficacy of AFI method has been evaluated in our study population, lower number of patients may cause a limitation in evaluation of the method efficacy.

Conclusion

Despite the absence of concomitant risk factors, OSA deteriorates LV systolic function, and the degree of deterioration is proportionate with the disease severity. By evaluating LV longitudinal functions with 2D-STE method, systolic dysfunction caused by OSA can be detected in the subclinical phase. Two-dimensional global longitudinal strain obtained with the AFI technology provides objective and quantitative assessments of LV function. It should prove to be superior to conventional measurements due to its independence of cardiac motion, tethering, and angle. We suggest that OSA patients are evaluated by conventional and newer echocardiographic methods so as not to overlook a subclinical cardiac functional impairment. Large scaled trials conducted on different OSA patients groups are necessary to evaluate LV systolic function effects, which are detected by AFI, on clinical outcomes and prognosis.

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