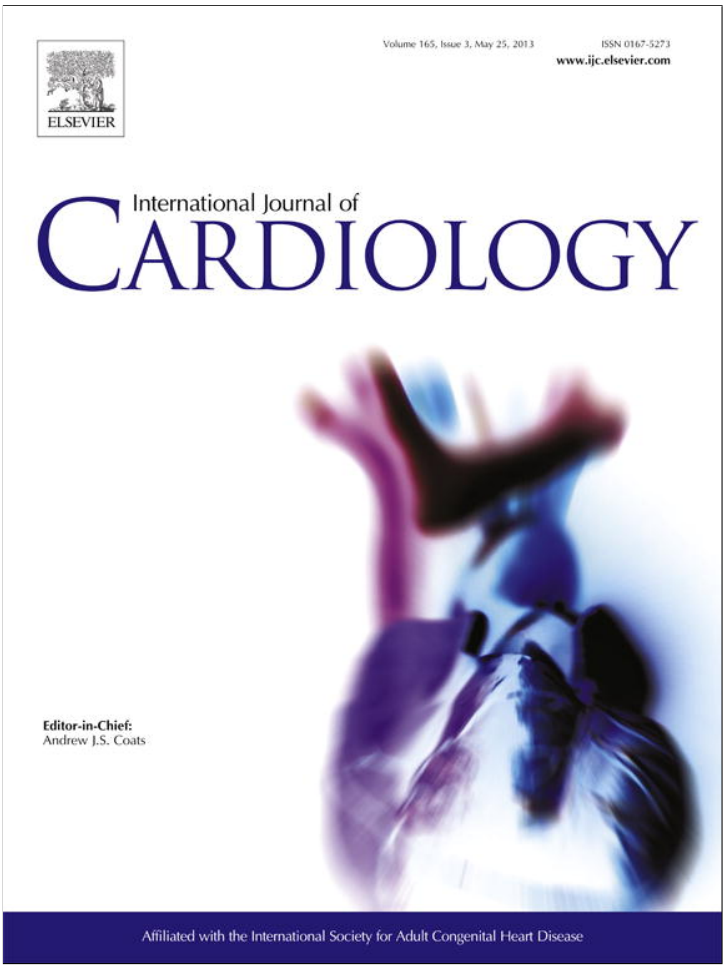
Provided for non-commercial research and education use.
Not for reproduction, distribution or commercial use.



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

http://www.elsevier.com/authorsrights

Author's personal copy

International Journal of Cardiology 165 (2013) 512–518

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Left ventricular torsion abnormalities in patients with obstructive sleep apnea syndrome: An early sign of subclinical dysfunction

Antonio Vitarelli *, Simona D'Orazio, Fiorella Caranci, Lidia Capotosto, Raymond Rucos, Gino Iannucci, Giovanna Continanza, Olga Dettori, Valentina De Cicco, Massimo Vitarelli, Melissa De Maio, Stefania De Chiara, Maurizio Saponara

Sapienza University, Rome, Italy

ARTICLE INFO

Article history:
Received 25 April 2011
Received in revised form 2 July 2011
Accepted 6 September 2011
Available online 2 October 2011

Keywords:
Obstructive sleep apnea syndrome
Echocardiography
Left ventricular function
Speckle tracking imaging
Aortic wall strain
Aortic wall stiffness

ABSTRACT

Background: Previous echocardiographic studies using tissue Doppler imaging (TDI) and speckle tracking imaging (STI) have demonstrated that obstructive sleep apnea syndrome (OSAS) patients may develop subclinical left ventricular (LV) systolic and diastolic dysfunction. Our purpose was to evaluate the impact of OSAS on LV torsion dynamics and aortic stiffness by using TDI and STI echocardiography.

Methods: Forty-two patients with OSAS and no comorbidities were studied. They were classified into mild and severe OSAS according to the apnea-hypopnea index (AHI). Thirty-five healthy subjects were selected as controls. Fifteen patients with severe OSAS underwent chronic nocturnal nasal continuous positive airway pressure (CPAP) therapy. Standard echocardiographic parameters were assessed. Global LV longitudinal strain (LS), radial and circumferential strain were determined by STI. Averaged LV rotation and rotational velocities from the base and apex were obtained and used for calculation of LV torsion (LVtor). Mitral annular velocities and aortic wall velocities and strain (AoS) were also obtained by TDI.

Results: Severe OSAS had decreased LS compared with control subjects. LVtor increased significantly in severe OSAS compared to normals ($p<.001$) as a result of a predominant increase in apical rotation and was independently related to AHI and AoS in a multiple stepwise linear regression model. The group treated with CPAP had a significant decrease in LVtor and aortic stiffness index and significant increase in LS and AoS.

Conclusions: LVtor, LS and AoS were identified as parameters demonstrating an association between LV dysfunction, aortic stiffness and severity of OSAS independently of other possible factors or comorbidities.

© 2011 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a sleep-related breathing disorder involving an increased risk of cardiovascular disease. OSAS has been recognized to impose several adverse effects on the cardiovascular system, to be associated with heart failure, and to represent an independent risk factor for hypertension [1,2]. Left ventricular (LV) hypertrophy and arterial dysfunction in OSAS have been reported even in the absence of systemic hypertension [3–7]. Previous echocardiographic studies using tissue-Doppler imaging (TDI) and speckle tracking imaging (STI) have demonstrated that OSAS patients may develop subclinical LV systolic and diastolic dysfunction [8–10]. Recently, STI has been validated as a noninvasive technique to quantify LV torsion dynamics, including the assessment of systolic torsion and diastolic filling versus magnetic resonance tagging [11–13]. Our purpose was to evaluate the impact of OSAS on LV torsion parameters and the relationship between these functional changes and aortic stiffness.

2. Methods

2.1. Population

A cohort of forty-two sleep apnea patients without systemic hypertension was identified among seventy-six people screened in the sleep disorder laboratory and examined with polysomnography and echocardiography. Thirty-five healthy subjects were matched for age, gender, and body mass index, and selected as controls. Subjects completed questionnaires on sleep habits and general health, and had height, weight, and blood pressure measured. A questionnaire to assess the Epworth sleepiness scale [4], which is a rapid, validated method for screening daytime sleepiness, was completed by all subjects. The inclusion criteria for control subjects were: [1] apnea-hypopnea index (AHI) <5 and [2] Epworth sleepiness scale <10. OSAS patients had to fulfill the following inclusion criteria: [1] AHI ≥15, [2] Epworth sleepiness scale ≥10, and [3] no previous treatment for OSAS. Patients with any of the following were excluded: central sleep apnea, systemic hypertension, any known cardiac disease (by history, physical examination, electrocardiogram, chest radiography, conventional stress testing, and echocardiography), atrial fibrillation, obstructive or restrictive lung disease (demonstrated on pulmonary function testing), pulmonary hypertension due to identifiable causes (except OSAS); chronic renal and hepatic diseases, diabetes mellitus (on history, or two random blood glucose levels >125 mg/dL), connective-tissue disease, and morbid

* Corresponding author at: Via Lima 35, 00198 Rome, Italy. Tel.: +39 06 85301427; fax: +39 06 8841926.
E-mail address: vitar@tiscali.it (A. Vitarelli).

0167-5273/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2011.09.030

Author's personal copy

obesity (body mass index >40 kg/m^2). Patients with poor echocardiographic window were also excluded when <80% of the endocardial border was adequately visualized.

2.2. Standard echocardiography

All patients underwent transthoracic echocardiography (Vivid E9 ultrasound system, GE, Horten, Norway). Measurements of cardiac chambers were made by transthoracic echocardiography according to established criteria [14]. LV ejection fraction by modified Simpson method and mass index were estimated [14,15]. Peak early (E) and late (A) diastolic velocities, deceleration time, left ventricular isovolumic relaxation time, myocardial performance index, and right ventricular systolic pressure were obtained using standard Doppler practices [16-18].

2.3. LV tissue Doppler imaging

The general principles that underlie the TDI modalities have been described previously [19]. Mitral annulus velocities (S_a, E_a, A_a) were measured on the transthoracic four chamber views. E/E_a ratio was used to estimate LV filling pressures and diastolic function [19–21].

2.4. LV speckle tracking imaging

Two-dimensional strain was measured as previously described [22,23]. After tracing endocardial border at an end-systolic frame, the operator could validate the tracking quality and adjust the endocardial border or modify the width of the region of interest. Aortic valve opening and closure were selected on pulsed-wave Doppler tracings recorded from the LV outflow tract. Frame rate ranged from 60 to 100 frame/s, and three cardiac cycles were stored in cineloop format for offline analysis. Longitudinal LV strain was defined as the average of negative longitudinal strains of 6 segments of the septal and lateral walls in the apical 4-chamber view (Fig. 1). Average radial and circumferential strain of 6 mid-LV segments was determined in the mid-short-axis view. The assessment of LV rotation by 2D speckle-tracking strain imaging required the acquisition of the LV short-axis at the basal and apical level. The basal level was defined as that which showed the mitral valve tip and the apical level as that which was just proximal to the level with LV cavity obliteration at end-systole. The time rotation curves were displayed along the cardiac cycle. Counterclockwise rotation was conventionally marked as positive value and clockwise rotation as negative value when viewed from the LV apex. Peak apical and basal rotation and peak LV torsion were obtained. LV torsion or twist (LVtor) was defined as the net difference (in degrees) of apical and basal rotation at isochronal time points. Normalized torsion was torsion divided by LV ventricular diastolic longitudinal length between apex and mitral plane. Peak diastolic untwisting velocity and time to peak untwisting velocity were measured. Twisting rate (TR) was defined [13] as (peak LVtor − LVtorEarlySystole)/(time difference between these two events). Untwisting rate (UTR) was defined as (peak LVtor − LVtorMVO)/(time difference between these two events) where MVO is mitral valve opening. The analysis of strain and rotation parameters was performed offline using customized computer software (EchoPAC, version 9.0, GE Ultrasound).

2.5. Aortic function

The elastic properties of the aorta were indexed by calculation [24–26] of aortic distensibility (D), stiffness index (SI), and pressure-strain elastic modulus (E_p) as $D = 2(A_s - A_d)/[A_d \quad (P_s - P_d)]$, $SI = \ln(P_s/P_d)/(A_s - A_d)/A_d$, and $E_p = (P_s - P_d)/[(A_s - A_d)/A_d]$, respectively, where A_s = aortic diameter at end-systole, A_d = aortic diameter at end-diastole, P_s = systolic blood pressure, P_d = diastolic blood pressure, and ln = natural logarithm.

Aortic wall TDI velocities have been obtained as previously described [27]. By marking a region of interest on the 2D image in the anterior aspect of the ascending aorta at the same point as in M-mode measurements, velocities throughout the cardiac cycle for this area can be determined. Offline analysis of the velocity data sets was performed using dedicated software (EchoPAC, version 9.0, GE Ultrasound). TDI tracing displayed accelerated expansion of the aortic wall followed by a slow deceleration, a plateau and then a rapid deceleration into diastole. This trace represents the mean of the instantaneous velocity spectrum. Systolic maximum wall expansion velocity (AoSvel, cm/s), wall contraction early diastolic velocity (AoEvel, cm/s), and wall peak systolic radial strain (AoS,%) were derived.

2.6. Sleep study

All patients underwent overnight polysomnography using a standard technique. A device measuring thoracic and abdominal respiratory movements and combined oronasal flow (PM unit, MAP, Martinsried, Germany) was attached to the patient. The following seven channels were monitored: [1] a flow sensor for joint registration of nasal and oral breath flow; [2] a laryngeal microphone; [3] a three-channel ECG; [4] one stress-sensitive belt for the thorax; [5] one stress-sensitive belt for the abdomen; [6] a positional sensor for determination of body position; [7] a pulse oximeter. A customer software (Poly-Mesam, version 1.42, MAP, Martinsried, Germany) gave the possibility to manually and/or automatically score the events on the raw data and analyze the graphical display.

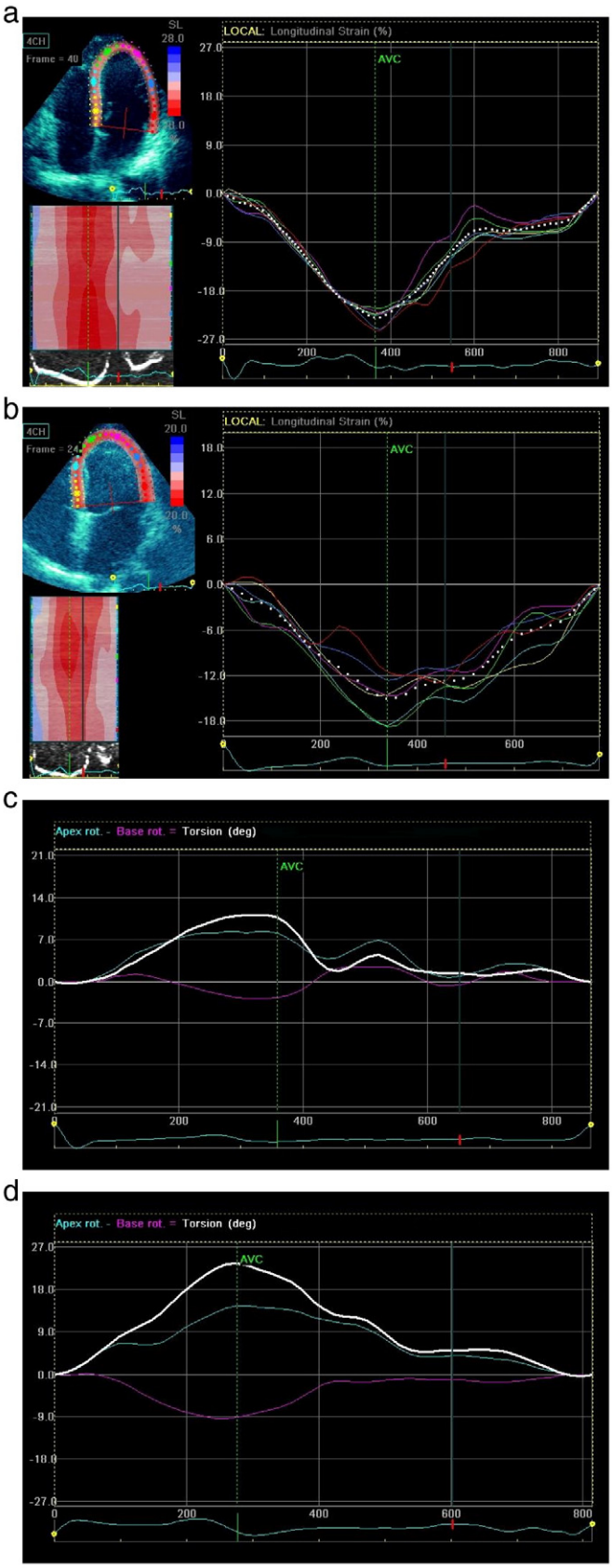


Fig. 1. Abnormal LV strain and torsion in OSAS patient compared to a normal control. 1a. Global LS (24%, white dotted line) in a normal control. 1b. Reduced global LS (13%, white dotted line) in a OSAS patient. 1c. Torsion (12, white solid line) in a normal control. 1d. Increased torsion (26, white solid line) in a OSAS patient. LS = longitudinal strain.

Author's personal copy

Apnea was defined [1,2] as complete cessation of air-flow for ≥10 s. Hypopnea was defined as a ≥50% reduction in air-flow lasting ≥10 s associated with a 4% decrease in nocturnal oxygen saturation (SaO_2) and a state of arousal. Apnea–hypopnea index (AHI) was defined as the number of apneas and/or hypopneas per hour. An obstructive apnea was defined as the absence of air-flow in spite of respiratory movement or exertion. A central sleep apnea was defined as the absence of both air-flow and respiratory movement. OSAS was defined as ≥5 AHI events per hour. On the basis of AHI patients were classified into mild (>5, <30) and severe (≥30) OSAS in line with previous reports [5,7,9]. Mean SaO_2, minimal SaO_2, and cumulative time with SaO_2 <90% during the study were also evaluated and recorded.

Fifteen patients with severe OSAS underwent chronic nocturnal nasal continuous positive airway pressure (CPAP) therapy. A CPAP titration sleep study was performed before baseline echocardiography and nasal CPAP pressure was adjusted so that apneas, hypopneas and respiratory effort-related arousal were abolished. All patients experienced a fall in AHI to fewer than five events per hour by the end of the CPAP titration sleep study. After the baseline echocardiogram, patients were instructed to use the CPAP device every night for at least 6 h. Adequate adherence to this prescribed pressure of CPAP was defined as more than 4.5 h of CPAP use per night. Patients subsequently received nightly nocturnal CPAP therapy for at least 4 months and the echocardiogram was repeated the day after the last nocturnal CPAP treatment while patients were awake.

2.7. Statistics

Data are presented as mean value ± SD. Linear correlations and analysis of variance were used for comparisons. Stepwise multiple regression analysis was performed to assess linear associations between LV torsion as dependent variable and determinants of clinical and cardiovascular parameters. Differences were considered statistically significant when the p value was <.05. To test intraobserver variability, STI and torsion measurements were made at different sites in different individuals on 2 different occasions. For interobserver variability, a second investigator randomly made measurements at the above different sites without knowledge of other echocardiographic parameters. The intraobserver and interobserver variabilities were determined (as the difference between the 2 sets of observations divided by the mean of the observations and expressed as a percentage).

3. Results

Forty-two out of 53 initially evaluated normotensive patients were included in the study. Though great care was taken to ensure the quality of the data collected, 19.2% of all wall segments had to be excluded from analysis as the strain traces were defined to be non-interpretable. The intraobserver and interobserver reproducibility of 2D-strain parameters was shown to be acceptable. The intraobserver and interobserver variation were 3.2% and 5.1% for mean LV long-strain, 5.5% and 8.3% for mean LV radial-strain, 5.3% and 10.7% for mean LV circum-strain, 7.5% and 11.8% for LV torsion, 9.2% and 14.6% for LV untwisting diastolic velocity. The patients' demographic data are given in Table 1. The main echocardiographic features in the controls and OSAS groups are compared in Table 2.

3.1. LV and aortic data in OSAS groups and controls

LV ejection fraction was not significantly different in OSAS patients and controls, and was in normal limits (Table 2). LV mass index and wall thickness were higher in severe OSAS than in the control group. RV end-diastolic area (RVEDA), RV end-systolic area (RVESA), and RV systolic pressure (RVSP) were higher in severe OSAS than in controls (19.6 ± 6.2 vs 14.8 ± 4.3 cm^2, 11.7 ± 3.1 vs 8.4 ± 2.1 cm^2, and 32 ± 7 vs 21 ± 4 mm Hg, respectively, $p<0.01$). LV diastolic function measurements such as mitral E_a, IVRT, and deceleration time were decreased in the severe OSAS group compared with the control group. MPI was increased in the same patient group compared to controls. Mild OSAS had no significant differences compared with control subjects. Severe OSAS had significantly decreased LV longitudinal strain and increased LVtor (Fig. 1) compared with control subjects. Calculation of the average longitudinal strain gave similar results regardless of the wall used to assess, i.e. 6 segments of the septal and lateral walls or 6 segments of the inferior and anterior walls or 12 segments of all 4 walls. LVtor increased significantly as a result of a predominant increase in apical rotation. LVtor and normalized LVtor values had a higher discriminating power in differentiating patients with severe OSAS from normals (Table 2). Peak diastolic untwisting velocity and untwisting rate were increased in severe OSAS (Table 2) as well as the time-to-peak diastolic untwisting velocity.

Diastolic aortic diameters were slightly increased in the severe OSAS group compared with control group (Table 2) but didn't reach a statistical significance. Aortic wall strain and distensibility were significantly decreased and stiffness index and elastic modulus significantly increased in the same patient group.

If we collected OSAS patients into mild and severe according to the AHI (AHI <30 and AHI ≥30, respectively), percent increase of LV torsion and percent reduction of LV longitudinal strain and Ao strain were significantly larger in the severe OSAS group (Fig. 2).

Correlation between LV torsion, LV strain and indexes of Ao function. LV-tor was positively related (Fig. 3) to AHI and negatively related to aortic wall peak systolic radial strain. A significant negative correlation existed between AHI and aortic strain (AoS) and between AHI and LV longitudinal strain (LVLS). When adjusted for potential confounding variables such as LV mass index, LVLS remained a significant predictor of AHI ($\beta = -0.38$, $p = 0.009$). LVtor was also directly

Table 1
Clinical characteristics of the study groups.

	Controls (n = 35)	Mild OSAS (n = 19)	p value[a]	Severe OSAS (n = 23)	p value[b]
Age	45.1 ± 12.2	48.3 ± 8.2	0.219	47.4 ± 8.1	0.306
Gender (male/female)	13/22	7/12	0.421	9/14	0.276
Smokers (n)	11	6	0.533	7	0.289
Body surface area (cm^2)	1.89 ± 0.17	1.91 ± 0.23	0.322	1.95 ± 0.25	0.219
Body mass index (kg/m^2)	26.8 ± 4.3	27.5 ± 5.4	0.218	28.3 ± 6.5	0.427
Heart rate (bpm)	69.7 ± 9.4	72.2 ± 7.4	0.235	70.6 ± 6.3	0.508
Systolic blood pressure (mm Hg)	120.3 ± 7.8	121.6 ± 8.2	0.202	122.8 ± 8.3	0.326
Diastolic blood pressure (mm Hg)	74.8 ± 5.9	76.7 ± 6.4	0.284	78.9 ± 6.5	0.487
Fasting blood glucose (mg/dL)	96.4 ± 9.3	101.7 ± 9.5	0.492	101.5 ± 11.3	0.276
Cholesterol (mg/dL)	168.3 ± 11.1	170.2 ± 9.4	0.336	172.3 ± 10.5	0.427
LDL-cholesterol (mg/dL)	87.9 ± 11.6	88.2 ± 15.4	0.612	89.1 ± 14.5	0.533
HDL-cholesterol (mg/dL)	39.1 ± 2.9	37.4 ± 3.1	0.483	35.9 ± 3.6	0.306
Triglyceride (mg/dL)	125.7 ± 15.3	124.5 ± 17.2	0.414	122.6 ± 19.8	0.323
Awake SaO_2 (%)	94.8 ± 2.1	93.7 ± 2.4	0.313	93.3 ± 2.3	0.247
AHI (events/h)	3.8 ± 1.1	15.4 ± 2.2	<0.005	59.4 ± 9.3	<0.001
Mean nocturnal SaO_2 (%)	93 ± 0.9	91.1 ± 13.7	0.211	82.6 ± 12.6	0.032
Minimal SaO_2 (%)	91 ± 0.6	80.4 ± 13.5	0.039	70.6 ± 12.3	<0.005
Time SaO_2 <90% (min)	0.6 ± 0.3	4.5 ± 1.2	0.043	31.7 ± 17.5	<0.005

AHI = apnea-hypopnea index; SaO_2 = saturation of arterial oxygen; time SaO_2 <90% = duration that oxygen saturation was <90%.
[a] Mild vs controls.
[b] Severe vs controls.

Author's personal copy

Table 2
LV and Ao findings in OSAS patients and controls.

Parameters	Controls (n = 35)	Mild OSAS (n = 19)	Severe OSAS (n = 23)	p values[a]
	Mean ± SD	Mean ± SD	Mean ± SD	
LV				
M-mode/2D/Doppler				
EF	0.62 ± 0.08	0.60 ± 0.07	0.59 ± 0.07	0.371
MI (g/m^2)	106 ± 5	113 ± 8	141 ± 11	0.023
IVRT (ms)	74 ± 11	103 ± 9	125 ± 10	0.041
DT (ms)	143 ± 14	175 ± 17	229 ± 15	0.047
MPI	0.39 ± 0.08	0.43 ± 0.07	0.58 ± 0.09	0.039
E/A	1.2 ± 0.5	1.1 ± 0.6	0.9 ± 0.5	0.071
TDI				
E_a (cm/s)	12.1 ± 2.2	11.4 ± 2.1	7.7 ± 2.8	0.016
E/E_a	5.6 ± 1.6	5.5 ± 1.8	8.8 ± 2.5	0.025
STI				
Global LS (%)	−21.9 ± 2.8	−21.2 ± 2.5	−18.4 ± 2.7	0.011
Global RS (%)	49.5 ± 9.8	49.9 ± 8.9	46.2 ± 9.1	0.278
Global CS (%)	−24.3 ± 3.1	−24.7 ± 2.4	−22.6 ± 3.1	0.432
Peak LVtor (°)	14.8 ± 4.2	15.7 ± 4.3	21.3 ± 5.1	<0.001
Peak apical rotation ( )	10.2 ± 3.4	10.9 ± 3.9	14.1 ± 4.1	<0.001
Peak basal rotation ( )	−6. ± 2.1	−6.7 ± 1.8	−7.6 ± 2.3	0.032
Normalized peak LVtor (/cm)	1.7 ± 0.4	1.8 ± 0.7	2.3 ± 0.6	<0.001
Peak UTV (/s)	78.5 ± 16	81.1 ± 14	97.2 ± 24	0.013
Normalized time to peak UTV (%)	16.2 ± 7.3	17.1 ± 5.8	22.3 ± 8.1	0.036
UTR (/s)	61.5 ± 27	63.1 ± 25	91.1 ± 32	0.048
Aorta				
AoES (mm)	29.2 ± 3.4	29.7 ± 3.1	30.3 ± 3.5	0.546
AoED (mm)	25.4 ± 3.1	26.1 ± 3.8	27.7 ± 3.6	0.638
AoSI	2.92 ± 0.76	3.21 ± 0.83	4.71 ± 1.42	0.031
AoEM (kPa)	30.2 ± 2.2	30.8 ± 2.5	45.4 ± 5.3	0.041
AoD (m^2/Newton)	75.3 ± 15.4	72.3 ± 14.4	48.3 ± 13.9	0.035
AoSvel (cm/s)	6.5 ± 0.6	6.2 ± 0.5	4.6 ± 0.4	0.014
AoEvel (cm/s)	7.3 ± 0.7	6.6 ± 0.7	4.2 ± 0.5	0.029
AoS (%)	15.4 ± 1.6	15.1 ± 1.7	7.2 ± 1.3	0.006

A = mitral inflow late diastolic velocity; AoD = aortic distensibility; AoED = aortic end-diastolic diameter; AoEM = aortic elastic modulus; AoES = aortic end-systolic diameter; AoEvel = aortic wall early diastolic velocity; AoS = aortic wall peak radial strain; AoSvel = aortic wall systolic velocity; AoSI = aortic stiffness index; CS = circumferential strain; DT = deceleration time; E = mitral inflow early diastolic velocity; E_a = annular early diastolic velocity; EF = ejection fraction; FS = fractional shortening; IVRT = isovolumic relaxation time; LS = longitudinal strain; LV = left ventricle; LVtor = left ventricular torsion; MI = mass index; RS = radial strain; time to peak UTV = time to peak untwisting velocity (expressed as percentage of duration of diastole); UTR = untwisting rate; UTV = untwisting diastolic velocity.
[a] Controls vs severe OSAS.

related (Table 3) to age, LVMI, relative wall thickness, E/Ea, pulmonary systolic pressure, and AHI, and inversely related to Ea and aortic wall strain. Multivariate analysis of these variables showed LVtor to be independently related ($R^2 = 0.65$) to AHI and aortic wall strain.

3.2. LV, aortic and polysomnographic data before and after CPAP

The effects of chronic 4 month CPAP therapy on the polysomnographic data and Doppler echocardiographic indexes of ventricular and aortic function are shown in Table 4. The CPAP was used for 6 ± 0.5 h per night (range, 5–6.4 h). The group treated with CPAP had a significant decrease in LV torsion, aortic stiffness index and pulmonary pressure, and significant increase in LV longitudinal strain and aortic wall velocity and strain. LV mass and aortic diameters did not decrease significantly in the CPAP group. The apnea-hypopnea index was virtually abolished (4.1 ± 1.8 events/h). An increase in mean and lowest arterial oxygen saturations, and a decrease in the duration of oxygen saturation below 90% were also seen.

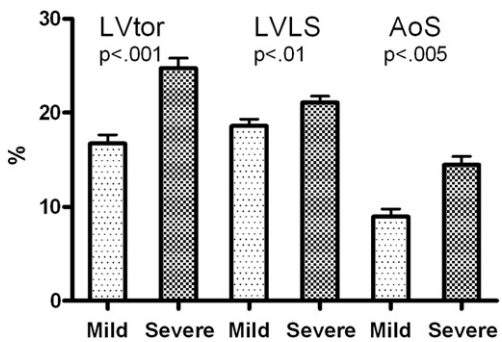


Fig. 2. Comparison of percent increase of LV torsion (LVtor) and per cent reduction of LV longitudinal strain (LS) and Ao strain (AoS) between the severe obstructive sleep apnea group (AHI ≥ 30) and the mild obstructive sleep apnea group (AHI < 30).

4. Discussion

OSAS can potentially accelerate the pathophysiology of congestive heart failure by producing detrimental effects on cardiac loading conditions and activation of the sympathetic nervous system [1, 2]. Respiratory efforts during obstructive episodes decrease intrathoracic pressure and increase left ventricular transmural pressure and afterload. Augmentation of venous return to the right heart may result in a leftward septal shift and reduced left ventricular preload and stroke volume. Activation of the sympathetic nervous system may result from recurrent arousal or profound hypoxia during apnea. This can lead to vasoconstriction, elevated peripheral resistance and an increased heart rate.

Our study shows that OSAS is associated with early signs of heart remodeling as demonstrated by increased LV torsion and decreased strain as well as increased arterial stiffness, and that arterial stiffness is an important factor associated with LV mass index and twist mechanics, suggesting a possible mechanism involved in heart remodeling in these patients. To the best of our knowledge, this is the first

Author's personal copy

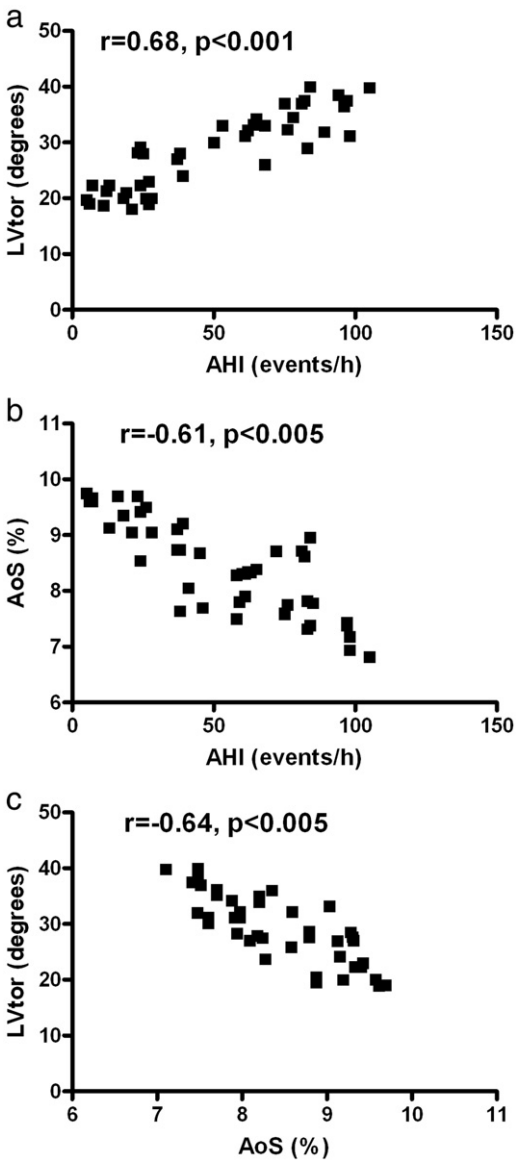


Fig. 3. Correlations between LV torsion and apnea-hypopnea index (3A, LVtor-AHI), Ao strain and apnea-hypopnea index (3B, AoS-AHI), and LV torsion and Ao strain (3C, LVtor-AoS).

study to evaluate the consequences of OSAS on LV torsion, the relationship between mechanical twist and aortic stiffness, and the response of LV torsion and aortic function to CPAP therapy.

Impairment of LV systolic and diastolic function and aortic stiffness were previously reported in patients with severe OSAS [3-10,28-30]. Since it is difficult to detect cardiac changes with conventional two-dimensional echocardiography before the clinical signs of LV dysfunction appear, TDI and STI have been used to represent an early stage of myocardial abnormality despite preserved global LV function [8-10]. An association between OSAS and impaired arterial properties in otherwise apparently healthy patients has also been reported [7]. Other studies [6,30] extended these findings by showing that vascular alterations associated with severe OSAS were similar but independent to that observed in systemic hypertension.

Interest in LV torsion, with regard to both its function and measurement, has increased in the past few decades [31–35]. Torsion is the description of the overall twisting motion of the ventricle around its long axis, calculated by determining the maximal apical rotation minus the maximal basal rotation. The significant association of the magnitude of LV torsion with the acceleration of the mitral E wave [32] introduced the concept that one of its main effects provides assistance to diastolic filling during elastic recoil by creating a suction effect. On the basis of these findings, torsion analysis may imply further insight into the presence of diastolic dysfunction [13,33,34]. Moreover, measurement may contribute to the overall assessment

Table 3
Analysis of LV torsion (LVtor) in OSAS patients.

Univariate analysis	r	p
Age	0.38	0.017
Sex	0.23	0.066
Smoking	0.11	0.721
BMI	0.34	0.057
BSA	0.27	0.072
SBP	0.17	0.367
RVSP	0.35	0.041
HR	0.12	0.619
LVEF	0.31	0.059
LVMI	0.44	0.024
LVRWT	0.42	0.037
E_a	−0.45	0.018
E/E_a	0.37	0.036
LVLS	−0.38	0.032
AoS	−0.64	0.007
AHI	0.68	0.002
Minimal SaO_2	−0.58	0.009
Multivariate analysis	**β**	**p**
AoS	−0.32	0.011
Minimal SaO_2	−0.46	0.004
AHI	0.53	0.003

AHI = apnea-hypopnea index; AoS = Ao strain; BMI = body mass index; BSA = body surface area; E = mitral inflow early-diastolic velocity; E_a = mitral annular early-diastolic velocity; HR = heart rate; LVLS = left ventricular longitudinal strain; LVMI = LV mass index; LVRWT = LV relative wall thickness; RVSP = right ventricular systolic pressure; SaO_2 = saturation of nocturnal arterial oxygen; SBP= systolic blood pressure.

Table 4
Change in ventricular and aortic indices and polysomnographic data in a subset of 15 patients who had chronic 4 month CPAP therapy.

	Before CPAP therapy	After CPAP therapy	p value
LVEF	0.58 ± 0.08	0.59 ± 0.07	0.454
LVMI (g/m^2)	141 ± 8	136 ± 9	0.239
LVE_a (cm/s)	7.3 ± 2.4	8.7 ± 2.3	0.018
LVMPI	0.55 ± 0.12	0.43 ± 0.09	0.032
RVEDA (cm^2)	19.6 ± 6.2	17.9 ± 5.1	0.042
RVFAC	0.46 ± 0.05	0.51 ± 0.04	0.029
RVSP (mmHg)	32 ± 7	26 ± 6	0.002
LVLS (%)	−18.3 ± 2.2	−20.2 ± 2.4	<0.001
LVRS (%)	46.1 ± 9.7	46.8 ± 9.2	0.362
LVCS (%)	−22.2 ± 3.5	−22.9 ± 3.7	0.687
LVtor (°)	23.5 ± 6.8	18.1 ± 6.2	<0.001
AoES (mm)	31.7 ± 3.1	31.4 ± 3.0	0.412
AoED (mm)	30.3 ± 3.2	29.9 ± 2.8	0.573
AoD (m^2/Newton)	48 ± 11	59 ± 10	0.033
AoSI	4.53 ± 1.49	3.29 ± 1.18	0.016
AoSvel (cm/s)	4.3 ± 0.4	5.1 ± 0.3	0.021
AoS (%)	7.5 ± 1.1	11.2 ± 1.3	0.002
AHI (events/h)	58.6 ± 9.4	4.1 ± 1.8	<0.001
Mean nocturnal SaO_2 (%)	89.5 ± 12.8	92.4 ± 13.3	0.003
Minimal SaO_2 (%)	70.4 ± 12.1	87.4 ± 13.1	<0.001
Time SaO_2 <90% (min)	31.1 ± 17.3	2.5 ± 2.9	<0.001
Awake SaO_2 (%)	93.4 ± 2.1	94.5 ± 1.8	0.261

AHI = apnea-hypopnea index; AoD = aortic wall distensibility; AoED = aortic end-diastolic diameter; AoES = aortic end-systolic diameter; AoSI = aortic wall stiffness index; AoS = aortic wall peak radial strain; AoSvel = aortic wall S-wave velocity; LVCS = LV circumferential strain; LVE_a = LV early diastolic mitral annular velocity; LVEF = LV ejection fraction; LVLS = LV longitudinal strain; LVMI = LV mass index; LVMPI = LV myocardial performance index; LVRS = LV radial strain; LVtor = LV torsion; RVEDA = RV end-diastolic area; RVFAC = RV fractional area change; RVSP = right ventricular systolic pressure; SaO_2 = saturation of arterial oxygen; time SaO_2 <90% = duration that oxygen saturation was <90%.

Author's personal copy

of LV systolic performance since systolic ventricular dysfunction is represented by significant changes in torsion [35].

In the present study, LV torsion and strain were identified as parameters demonstrating an association between LV dysfunction and severity of OSAS independently of body mass index, diabetes mellitus, and systemic arterial hypertension. Both ventricular twist and diastolic untwisting were abnormal in our patients. It has been shown that LVtor is increased in patients with mild diastolic dysfunction and is normalized in more advanced diastolic dysfunction compared with healthy controls [13], whereas in patients with severe diastolic dysfunction torsion and untwisting are markedly reduced [36, 37]. A paradoxically increased LV torsion with normal EF has been reported as an early indicator of LV dysfunction in patients with aortic stenosis, diabetes, hypertrophic cardiomyopathy, and systemic hypertension [38–41]. The increased torsion and subsequent untwisting may be a compensatory mechanism for the reduced longitudinal myocardial contraction as well as relaxation to maintain normal LV filling. Increased LVtor seems to be a part of natural progression of systo-diastolic dysfunction as an initial compensation and has also been reported in asymptomatic elderly patients with mild diastolic dysfunction compared to younger individuals [42]. Subendocardial function may gradually attenuate with increasing age, and LV twist increases because of an unopposed increase in LV apical rotation. The velocity of untwisting in early diastole is also involved. LV untwisting starts near the end-systole and lasts throughout the isovolumic period until mitral valve opening, that is a critical interval for LV pressure decay and chamber filling. Delayed diastolic events and depressed untwisting reflect ineffective myocardial uncoiling whereas delayed but increased untwisting such as in our patients implies a mild diastolic dysfunction with more effective uncoiling. This is in line with previous reports [41] showing that in hypertrophic cardiomyopathy peak diastolic untwisting velocity and untwisting rate were increased in mild but decreased in moderate and severe diastolic dysfunction.

Analysis of LV long-axis function and strain may provide an additional explanation of the mechanism of LV torsion. It has been shown that in hypertensive patients with normal ejection fraction [40] impaired longitudinal strain and increased LV torsion correlated with serum tissue inhibitor of matrix metalloproteinase, suggesting that myocardial fibrosis may affect the early contractile LV dysfunction. Longitudinal fibers, as a consequence of their prominent subendocardial location, are more vulnerable to hemodynamic overload compared to mid wall circular fibers. In our study OSAS patients with normal EF were found to have increased LVtor and mild diastolic impairment together with reduced systolic longitudinal strain compared to normal controls. This is further evidence that hypertorsion and subsequent untwisting appear as a compensatory mechanism for the reduced myocardial long-axis function to keep normal LV filling.

Another interesting result we obtained is the significant relationship between LV torsion and ascending aorta wall strain. Aortic parameters determined from echocardiography of ascending aorta (aortic strain and distensibility) have been used for measuring the large arterial stiffness. Several reports have shown good correlations between aortic function indices calculated from aortic root and indices derived from aortography and pulse wave analysis methods [24–27]. Early signs of atherosclerosis have been described in patients with OSAS who were free of systemic hypertension or other significant comorbidities [43,44]. Other studies have shown that the treatment of OSAS with CPAP therapy improves markers of early signs of atherosclerosis such as carotid intima-media thickness and arterial stiffness [30]. The effects of CPAP therapy on the early signs of atherosclerosis are multifactorial and are associated with improvements in inflammation and sympathetic activity. Our study was not specifically designed to assess the effects of CPAP on all the mechanisms involved in atherosclerosis progression. However, we found an inverse relationship between increased LV torsion and reduced aortic strain and an improvement in LV torsion with CPAP therapy that was associated with the change in aortic stiffness during the same treatment. This is in agreement with previous reports [28] which showed that the improvement in left ventricular systolic function with chronic CPAP therapy appeared to relate to the baseline systemic vascular resistance index and the change in systemic resistance during therapy through a reduction of sympathetic nervous system activity. Whether improvements in torsion and arterial indexes translate into an improvement in patient prognosis remains to be answered.

No regression in LV mass was observed in our patients after CPAP treatment. We were not able to determine whether longer therapy might have resulted in a more significant reversal of diastolic abnormalities since it has been reported regression of ventricular hypertrophy after a minimum of 6 months with CPAP [4]. However diastolic dysfunction can occur in the absence of structural myocardial abnormalities both in OSAS and hypertensive patients and may represent myocyte dysfunction with impaired isovolumic relaxation [7].

A partial regression of RV dysfunction and pulmonary hypertension has been obtained in our patients after CPAP. AHI has been reported to be the parameter that had the closest correlation with RVSP level and a relationship was found between LV diastolic dysfunction and pulmonary hypertension [45]. It may be hypothesized a vicious pathophysiologic cycle in which the contribution of LV diastolic dysfunction to the development of pulmonary hypertension seems to be likely [45]. It has also been suggested that OSAS affects RV function independently of pulmonary pressure [46]. A further study specifically aimed at RV involvement in these patients would be desirable.

Limitations. A technical limitation is that speckle-tracking echocardiography is dependent both on frame rate and image resolution [22,23]. This may be challenging in the presence of obesity/pulmonary conditions associated with OSAS limiting 2D visibility. In addition, the endocardial border tracing must be manually optimized. Speckle pattern changes too much from frame to frame because of low frame rates, and this prevents the precise characterization of regional myocardial motion and impairs the overall temporal resolution of the regional strain map. On the contrary, increasing the frame rate reduces scan line density that reduces image resolution. We found frame rates in the range of 60 to 100 Hz suitable for speckle-tracking analysis, that is a lower value than frame rate available with Doppler strain. However, STI may overcome some TDI limitations by assessing myocardial thickening in a manner less affected by passive translational motion or tethering.

Also we have not directly estimated the exact distance between the two short-axis levels, which could have affected LVtor measurements, nor have we selected reproducible anatomic landmarks for measuring apical rotation although we defined the apical level just proximal to the level with LV luminal obliteration at the end-systolic period [11].

Moreover, we only included patients with OSAS who were free of significant comorbidities. The results of this study may not be extrapolated to patients with overt comorbidities which could act as confounding factors and influence all measurements. However, recent studies reported that the magnitude of arterial stiffness and heart remodeling associated with OSAS is similar to that for treated hypertension and OSAS associated with hypertension had additive effects on LV dysfunction and arterial stiffness [6,7,44].

A final limitation was the relatively small population. Sample size limited our ability to draw definitive conclusions regarding the benefit of torsion analysis in selected patient subsets and a larger study is needed to corroborate our data. However we succeeded in testing our hypothesis, which showed functional information from LV torsion parameters in OSAS patients.

4.1. Conclusions

Left ventricular impaired twist mechanics is frequently observed in OSAS patients and is associated with increased aortic stiffness,

Author's personal copy

which suggests that it may be an early response to cardiac overload caused by this disease independently of other possible factors. Chronic application of CPAP may avoid the progression of systo-diastolic abnormalities and reverse these alterations before severe ventricular structural changes develop. We suggest that these patients are screened by standard and newer echocardiographic parameters so as not to overlook a clinically silent cardiac functional impairment. Further studies are required to assess the long-term impact of these more recent echocardiographic variables on the diagnosis of myocardial dysfunction in OSAS patients.

Acknowledgment

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

References

[1] Khayat R, Patt B, Hayes Jr D. Obstructive sleep apnea: the new cardiovascular disease. Part I: obstructive sleep apnea and the pathogenesis of vascular disease. Heart Fail Rev 2009;14:143–53.
[2] Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation 2010;122:352–60.
[3] Cloward TV, Walker JM, Farney RJ, Anderson JL. Left ventricular hypertrophy is a common echocardiographic abnormality in severe obstructive sleep apnea and reverses with continuous positive airway pressure. Chest 2003;124:594–601.
[4] Dursunoglu D, Dursunoglu N, Evrengul H, et al. Impact of obstructive sleep apnoea on left ventricular mass and global function. Eur Respir J 2005;26:283–8.
[5] Tomiyama H, Takata Y, Shiina K, et al. Concomitant existence and interaction of cardiovascular abnormalities in obstructive sleep apnea subjects with normal clinic blood pressure. Hypertens Res 2009;32:201–6.
[6] Tavil Y, Kanbay A, Sen N, et al. The relationship between aortic stiffness and cardiac function in patients with obstructive sleep apnea, independently from systemic hypertension. J Am Soc Echocardiogr 2007;20:366–72.
[7] Drager LF, Bortolotto LA, Figueiredo AC, Silva BC, Krieger EM, Lorenzi-Filho G. Obstructive sleep apnea, hypertension, and their interaction on arterial stiffness and heart remodeling. Chest 2007;131:1379–86.
[8] Kasikcioglu HA, Karasulu L, Tartan Z, Kasikcioglu E, Cuhadaroglu C, Cam N. Occult cardiac dysfunction in patients with obstructive sleep apnea syndrome revealed by tissue Doppler imaging. Int J Cardiol 2007;118:203–5.
[9] Haruki N, Takeuchi M, Nakai H, et al. Overnight sleeping induced daily repetitive left ventricular systolic and diastolic dysfunction in obstructive sleep apnoea: quantitative assessment using tissue Doppler imaging. Eur J Echocardiogr 2009;10: 769–75.
[10] Haruki N, Takeuchi M, Kanazawa Y, et al. Continuous positive airway pressure ameliorates sleep-induced subclinical left ventricular systolic dysfunction: demonstration by two-dimensional speckle-tracking echocardiography. Eur J Echocardiogr 2010;11:352–8.
[11] Kim HK, Sohn DW, Lee SE, et al. Assessment of left ventricular rotation and torsion with two-dimensional speckle tracking echocardiography. J Am Soc Echocardiogr 2007;20:45–53.
[12] Shaw SM, Fox DJ, Williams SG. The development of left ventricular torsion and its clinical relevance. Int J Cardiol 2008;130:319–25.
[13] Park SJ, Miyazaki C, Bruce CJ, Ommen S, Miller FA, Oh JK. Left ventricular torsion by two-dimensional speckle tracking echocardiography in patients with diastolic dysfunction and normal ejection fraction. J Am Soc Echocardiogr 2008;21: 1129–37.
[14] Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
[15] Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450–8.
[16] Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler quantification task force of the nomenclature and standards committee of the American Society of Echocardiography. J Am Soc Echocardiogr 2002;15:167–84.
[17] Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107–33.
[18] Nagueh SF, Bhatt R, Vivo RP, et al. Echocardiographic evaluation of hemodynamics in patients with decompensated systolic heart failure. Circ Cardiovasc Imaging 2011;4:220–7.
[19] Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788–94.
[20] Hummel YM, Klip IJ, de Jong RM, Pieper PG, van Veldhuisen DJ, Voors AA. Diastolic function measurements and diagnostic consequences: a comparison of pulsed wave- and color-coded tissue Doppler imaging. Clin Res Cardiol 2010;99:453–8.
[21] Takamura T, Onishi K, Sugimoto T, et al. Patients with a hypertensive response to exercise have impaired left ventricular diastolic function. Hypertens Res 2008;31: 257–63.
[22] Korinek J, Wang J, Sengupta PP, et al. Two-dimensional strain — a Doppler independent ultrasound method for quantitation of regional deformation: validation in vitro and in vivo. J Am Soc Echocardiogr 2005;18:1247–53.
[23] Amundsen BH, Helle-Valle T, Edvardsen T, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 2006;47: 789–93 (STI).
[24] Stefanadis C, Stratos C, Boudoulas H, Kourouklis C, Toutouzas P. Distensibility of the ascending aorta: comparison of invasive and non-invasive techniques in healthy men and in men with coronary artery disease. Eur Heart J 1990;11:990–6.
[25] Schmidt-Trucksass A, Grathwohl D, Schmid A, et al. Assessment of carotid wall motion and stiffness with tissue Doppler imaging. Ultrasound Med Biol 1998;24: 639–46.
[26] Mottram PM, Haluska BA, Leano R, Carlier S, Case C, Marwick TH. Relation of arterial stiffness to diastolic dysfunction in hypertensive heart disease. Heart 2005;91: 1551–6.
[27] Vitarelli A, Giordano M, Germanò G, et al. Assessment of ascending aorta wall stiffness in hypertensive patients by tissue Doppler imaging and strain Doppler echocardiography. Heart 2010;96:1469–74.
[28] Johnson CB, Beanlands RS, Yoshinaga K, et al. Acute and chronic effects of continuous positive airway pressure therapy on left ventricular systolic and diastolic function in patients with obstructive sleep apnea and congestive heart failure. Can J Cardiol 2008;24:697–704.
[29] Akar Bayram N, Ciftci B, Durmaz T, et al. Effects of continuous positive airway pressure therapy on left ventricular function assessed by tissue Doppler imaging in patients with obstructive sleep apnoea syndrome. Eur J Echocardiogr 2009;10: 376–82.
[30] Drager LF, Bortolotto LA, Figueiredo AC, Krieger EM, Lorenzi GF. Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea. Am J Respir Crit Care Med 2007;176:706–12.
[31] Helle-Valle T, Crosby J, Edvardsen T, et al. New noninvasive method for assessment of left ventricular rotation: speckle tracking echocardiography. Circulation 2005;112:3149–56.
[32] Rothfeld JM, LeWinter MM, Tischler MD. Left ventricular systolic torsion and early diastolic filling by echocardiography in normal humans. Am J Cardiol 1998;81: 1465–9.
[33] Rüssel IK, Götte MJ, Bronzwaer JG, Knaapen P, Paulus WJ, van Rossum AC. Left ventricular torsion: an expanding role in the analysis of myocardial dysfunction. JACC Cardiovasc Imaging 2009;2:648–55.
[34] Vitarelli A, Capotosto L, Rosato E, Salsano F. Echocardiographic myocardial imaging reveals segmental cardiomyopathy in Churg–Strauss syndrome. Tex Heart Ins J 2010;37:594–7.
[35] Popescu BA, Beladan CC, Calin A, et al. Left ventricular remodelling and torsional dynamics in dilated cardiomyopathy: reversed apical rotation as a marker of disease severity. Eur J Heart Fail 2009;11:945–51.
[36] Tan YT, Wenzelburger F, Lee E, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol 2009;54:36–46.
[37] Lam W, Leano R, Haluska B, Marwick TH. Effects of myocardial ischaemia on left ventricular untwist and filling pressure. Heart 2011;97:757–61.
[38] van Dalen BM, Tzikas A, Soliman OI, et al. Left ventricular twist and untwist in aortic stenosis. Int J Cardiol 2011;148:319–24.
[39] Shivu GN, Abozguia K, Phan TT, et al. Increased left ventricular torsion in uncomplicated type 1 diabetic patients: the role of coronary microvascular function. Diabetes Care 2009;32:1710–2.
[40] Kang SJ, Lim HS, Choi BJ, et al. Longitudinal strain and torsion assessed by two-dimensional speckle tracking correlate with the serum level of tissue inhibitor of matrix metalloproteinase-1, a marker of myocardial fibrosis, in patients with hypertension. J Am Soc Echocardiogr 2008;21:907–11.
[41] van Dalen BM, Kauer F, Michels M, et al. Delayed left ventricular untwisting in hypertrophic cardiomyopathy. J Am Soc Echocardiogr 2009;22:1320–6.
[42] van Dalen BM, Soliman OI, Vletter WB, ten Cate FJ, Geleijnse ML. Age-related changes in the biomechanics of left ventricular twist measured by speckle tracking echocardiography. Am J Physiol Heart Circ Physiol 2008;295:H1705–11.
[43] Drager LF, Bortolotto LA, Lorenzi MC, Figueiredo AC, Krieger EM, Lorenzi-Filho G. Early signs of atherosclerosis in obstructive sleep apnea. Am J Respir Crit Care Med 2005;172:613–8.
[44] Drager LF, Bortolotto LA, Krieger EM, Lorenzi-Filho G. Additive effects of obstructive sleep apnea and hypertension on early markers of carotid atherosclerosis. Hypertension 2009;53:64–9.
[45] Arias MA, García-Río F, Alonso-Fernández A, Martínez I, Villamor J. Pulmonary hypertension in obstructive sleep apnoea: effects of continuous positive airway pressure. A randomized, controlled cross-over study. Eur Heart J 2006;27:1106–13.
[46] Romero-Corral A, Somers VK, Pellikka PA, et al. Decreased right and left ventricular myocardial performance in obstructive sleep apnea. Chest 2007;132:1863–70.