

## Early Left Ventricular Function Abnormalities in Obstructive Sleep Apnea

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### Abstract

**Introduction:** Our aim was to assess by Tissue Doppler Imaging (TDI) the early left ventricular (LV) myocardial function abnormalities in obstructive sleep apnea (OSA).

**Methods:** Thirty four patients (11 females, 23 males, aged 25-51) with newly diagnosed, nontreated OSA and normal echocardiographic parameters of LV diastolic and systolic function were investigated. The patients with known cardiovascular or respiratory disease were excluded. The LV end-systolic longitudinal strain (LS), peak-systolic longitudinal strain rate (LSR) and isovolumetric acceleration (IVA) of the septal and lateral mitral annulus was evaluated by TDI. Twenty two healthy persons (9 women, 13 men, and aged 23-48) were assessed as controls.

**Results:** All OSA patients demonstrated significant decrease of the LV end-systolic LS:  $-15.7 \pm 0.42\%$  vs controls:  $-18.9 \pm 0.56\%$  ( $p < 0.01$ ) and LV peak-systolic LSR:  $1.72 \pm 0.63 \text{ s}^{-1}$  vs  $3.19 \pm 0.68 \text{ s}^{-1}$ , respectively ( $p < 0.001$ ). The IVA was also reduced: the septal mitral annulus:  $-2.82 \pm 0.45 \text{ cm/sec}$  in OSA vs  $-4.03 \pm 0.6 \text{ cm/sec}$  in healthy subjects ( $p < 0.01$ ) and the lateral mitral annulus:  $-3.37 \pm 0.54 \text{ cm/sec}$  in gr. I vs  $-4.29 \pm 0.42 \text{ cm/sec}$  in gr. II ( $p < 0.01$ ).

**Conclusions:** Tissue Doppler Imaging might be a reliable method for detection of early abnormalities in LV function in patients with OSA. Reduction of longitudinal strain, strain rate and isovolumetric acceleration might be present in patients with OSA, even without overt diastolic or systolic LV dysfunction. Further studies with larger sample size are needed.

**Keywords:** Tissue doppler imaging; Left ventricular function; Obstructive sleep apnea

### Introduction

Obstructive sleep apnea (OSA) is a significant major healthcare and public problem, affecting general population worldwide and its importance increases with the growing number of patients with obesity [1]. Pathophysiologically OSA is characterized by repeated episodes of partial or complete collapse of the upper airways during sleep, together with gasping episodes, more than 10 second pauses in respiration associated with increasing ventilatory effort, daytime sleepiness, abnormal nocturnal arousals and oxyhaemoglobin desaturation. Generally, OSA syndrome is accepted when patient has an apnea-hypopnea index over 5 per night and symptoms of excessive daytime sleepiness [2].

Emerging data suggest that OSA may be associated with and contributes to a vast majority of cardiovascular diseases (CVD), including systemic and pulmonary hypertension, acute myocardial infarction, rhythm disorders, stroke and sudden cardiovascular death [3]. Moreover, the patients may remain asymptomatic from apneas, presenting instead with hypertension, nocturnal arrhythmias or

congestive heart failure. According to some of the last trials, about 85% of patients with clinically significant and treatable OSA are not diagnosed and this population of OSA cases represents only the “tip of the iceberg” of OSA prevalence [4].

Regardless of the fact the underlying mechanisms are not known, it is suggested that the cardiovascular effects of OSA have multiple pathological pathways [4-7]. In general, the increased cardiovascular risk can be declared to recurrent hypoxia, hypercapnia, acidosis, increased sympathetic activity and impairment of balance between myocardial oxygen demand and supply during sleep [6]. A recent study in which participated 6000 adults (Sleep Heart Health Study) noted that hypopneas, accompanied by oxyhemoglobin desaturation, were associated with prevalent cardiovascular disease, independently of the accompanied comorbidities [8]. In contrast, no association was observed between cardiovascular disease and hypopneas, accompanied by milder desaturation or arousals.

As for the clinical practice nowadays there is a variety of methods to diagnose OSA's effects on cardiovascular system: blood tests analysis, electrocardiography (ECG), ambulatory or nocturnal blood pressure monitoring, heart rate variation analysis, and echocardiography. Screening of OSA patients for CVD, although the sensitivity and specificity have not been well defined, includes: Epworth Sleepiness

Scale, the Berlin questionnaire, overnight oximetry and devices combining: limited respiratory assessment, ECG and oximetry.

In this setting, Tissue Doppler Imaging (TDI) echocardiography is an important tool to assess the overt systolic and diastolic left ventricular (LV) dysfunction in OSA patients [2]. In TDI, Doppler principles are used to quantify the higher-amplitude, low-velocity signals of myocardial tissue motions [9]. Tissue velocities assessment and strain evaluation provide detailed visual and quantitative information about regional and global mechanics and offer essential additional data on myocardial function compared to conventional echocardiography [10]. The real value of TDI for detection of early LV function abnormalities remains not well defined.

## Objective

Our aim was to investigate by Tissue Doppler Imaging the early left ventricular function changes in patients with obstructive sleep apnea and echocardiographic evidence for normal diastolic and systolic LV function.

## Material and methods

### Patients and procedures

Thirty four persons (11 females and 23 males, aged 25-51 years) with newly diagnosed by polysomnography and nontreated OSA were evaluated (Group I). The patients with arterial or pulmonary hypertension, as well as known cardiovascular or respiratory disease were excluded from the study. All patients underwent a night of diagnostic polysomnography, assessed and interpreted by Compumedix ProFusion PSG 3 system. The record was performed in minimum 6 hours of constant monitoring and involves 7 measurement parameters (1 or 2 channel electroencephalogram, 2 channel electrooculogram, 2 muscle electromyogram, ECG, oxygen saturation, airflow monitoring, and measures of breathing/respiratory effort). The polysomnographic measurements were scored according to the accepted standard criteria. OSA was confirmed when more than 15 obstructive events per hour were registered or had more than 5 obstructive events per hour plus clinical symptoms. Obstructive events included: apneas, hypopneas, or respiratory event-related arousals. Clinical symptoms were as follows: unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue, insomnia, waking up breath holding, gasping, or choking, or the bed

partner describes loud snoring, breathing interruptions, or both during the patient's sleep [11,12]. The average apnea/hypopnea index (AHI) was also calculated - 21 for the group I, which corresponded to moderate OSA.

All involved OSA patients had normal structural parameters from M-mode and 2D transthoracic echocardiography. The LV diastolic and systolic function indices, assessed by Doppler-echocardiography according to the recommendations of the European Society of Echocardiography were in normal ranges [13,14].

The LV end-systolic longitudinal strain (LS) in the grey scale, peak-systolic longitudinal strain rate (LSR) and isovolumetric acceleration (IVA) of the septal and lateral mitral annulus were evaluated by Tissue Doppler Imaging (TDI) with the purpose to detect some possible early changes in the left ventricular function [13].

Twenty two healthy persons, (9 women and 13 men, aged 23-48 years) without a history or symptoms of sleep-related disorders and cardiovascular diseases were assessed as controls (group II).

### Statistics

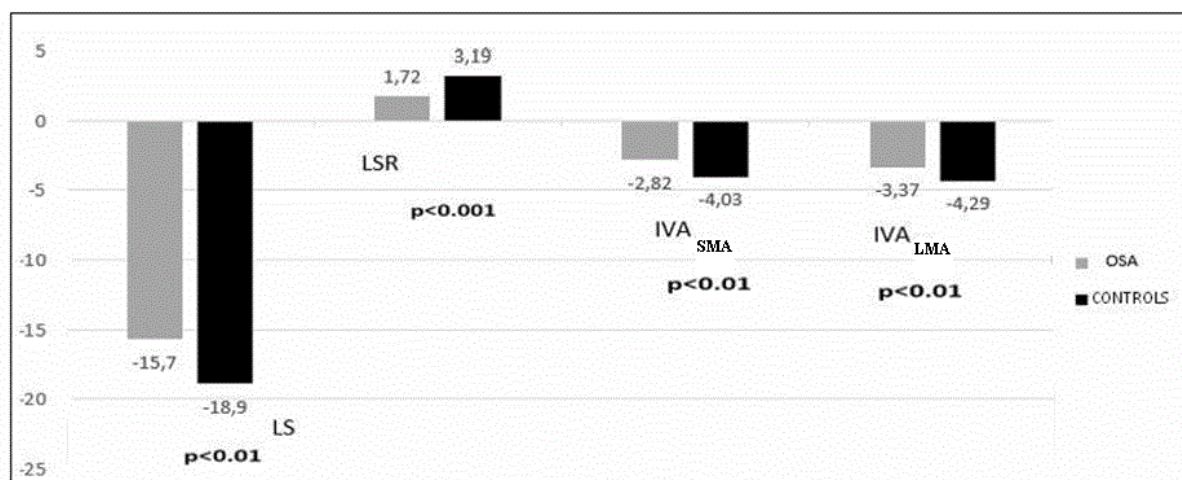
Statistical analysis was performed using SPSS version 12.00. All measured variables were expressed as means  $\pm$  SD. A Kolmogorov-Smirnov test was applied to find if a normal distribution existed. The comparison of variables between the two studied groups was performed by one way analysis of variance (ANOVA). As a level of statistical significance was considered  $p < 0.05$ .

### Results

The patients in both studied groups had similar mean age:  $43 \pm 3.7$  years in gr. I vs  $41 \pm 4.9$  years in gr. II,  $p = \text{NS}$ . The mean body mass index in gr. I ( $31.4 \pm 3.2 \text{ kg/m}^2$ ) was higher in comparison to gr. II ( $26.3 \pm 2.6 \text{ kg/m}^2$ ,  $p < 0.05$ ). All patients, suffering from OSA, demonstrated significant decrease of the LV end-systolic LS:  $-15.7\% \pm 0.42\%$  vs controls:  $-18.9\% \pm 0.56\%$  ( $p < 0.01$ ) and LV peak-systolic LSR:  $1.72 \pm 0.63 \text{ s}^{-1}$  vs  $3.19 \pm 0.68 \text{ s}^{-1}$ , respectively ( $p < 0.001$ ). The isovolumetric acceleration, performed by TDI, was also reduced: the septal mitral annulus:  $-2.82 \pm 0.45 \text{ cm/sec}$  in OSA patient's vs  $-4.03 \pm 0.6 \text{ cm/sec}$  in healthy subjects ( $p < 0.01$ ) and the lateral mitral annulus:  $-3.37 \pm 0.54 \text{ cm/sec}$  in gr. I vs  $-4.29 \pm 0.42 \text{ cm/sec}$  in gr. II ( $p < 0.01$ ) (Table 1 and Figure 1)

Parameters	OSA patients (gr. I)	Controls (gr. II)	p
Age (years)	$43 \pm 3.7$	$41 \pm 4.9$	NS
Body Mass Index	$31.4 \pm 3.2 \text{ kg/m}^2$	$26.3 \pm 2.6 \text{ kg/m}^2$	$p < 0.05$
Left ventricular end-systolic longitudinal strain	$-15.7\% \pm 0.42\%$	$-18.9\% \pm 0.56\%$	$p < 0.01$
Left ventricular peak-systolic longitudinal strain rate	$1.72 \pm 0.63 \text{ s}^{-1}$	$3.19 \pm 0.68 \text{ s}^{-1}$	$p < 0.001$
Isovolumetric acceleration (septal mitral annulus)	$-2.82 \pm 0.45 \text{ cm/sec}$	$-4.03 \pm 0.6 \text{ cm/sec}$	$p < 0.01$
Isovolumetric acceleration (lateral mitral annulus)	$-3.37 \pm 0.54 \text{ cm/sec}$	$-4.29 \pm 0.42 \text{ cm/sec}$	$p < 0.01$

**Table 1:** Main results of the studied parameters in patients with obstructive sleep apnea and in controls



**Figure 1:** Comparative analysis of LV end-systolic longitudinal strain (LS), peak-systolic longitudinal strain rate (LSR) and isovolumetric acceleration of the septal and lateral mitral annulus (IVASMA, IVALMA), evaluated by Tissue Doppler Imaging (TDI) in the both studied groups.

## Discussion

The syndrome of OSA and cardiovascular diseases have close interaction in pathogenetic and pathophysiologic aspects and often appear to be underdiagnosed and undertreated [34]. Doherty et al. suggested that untreated OSA might increase rather the severity than the prevalence of CVD [7]. It was proven that OSA could contribute to the development of LV morphologic abnormalities, caused by changes in LV afterload, intermittent hypoxemia, constant catecholaminergic hyperactivity, oxidative stress and recurrent arousals during sleep. Left ventricular diastolic dysfunction often precedes and leads to systolic impairment and accounts for 30–40% of patients with LV failure [16]. Patients with OSA usually exhibit with normal ejection fraction (EF). However, normal value of EF does not always exclude LV systolic dysfunction [17]. Hypoxia, in addition, may also precipitate the induction of subendocardial ischemia, resulting in a decrease of systolic function.

Early morphological changes in myocardial tissue and kinetics, without downright global dysfunction cannot be detected by routine echocardiographic observation. The method with proven evidence was affirmed to be TDI.

Today some controversies regarding LV systolic function in OSA exist. Haruki et al. reported that OSA was associated with both development of subclinical systolic LV dysfunction and worsened pre-existing diastolic dysfunction, assessed by TDI [17]. Results of the study of Kasikcioglu H. et al. suggested that TDI could demonstrate the early myocardial abnormalities despite preserved global LV ejection function. In patients with OSA who had normal LV function, septal Sm and Em velocities and Em/Am ratio were found to be lower than the control group, i.e. a myocardial dysfunction was detected [1]. Alchanatis et al. evaluated LV function in obese patients with or without OSA and reported that LV diastolic function was impaired in cases with OSA [18]. In Bayram N. et al. study decreased velocities of LV septal and lateral wall, as well as lower Em/Am ratio were found in patients with OSA [5]. An investigation, conducted in Antwerp, Belgium, demonstrated that the higher apnea/hypopnea index

correlated significantly with reduced TDI-derived velocities, measured at the mitral, tricuspid annulus and right ventricular free wall, as well as with the lower stroke volume [15]. Dursunoglu D. et al. estimated left ventricular mass index (LVMI) and global LV function in OSA patients with preserved LVEF. They detected a significant positive correlation between myocardial performance index and the severity of OSA, assessed by AHI [3]. The hypothesis of a direct link between OSA and daytime LV dysfunction was consolidated by the fact that a normalization of LV systolic function after OSA treatment might occur [19].

Another TDI parameter, isovolumetric acceleration (IVA) of the septal and lateral mitral annulus, was introduced as a novel, easily obtained, noninvasive index of myocardial contractile state. Results from animal studies indicated that IVAs seem unaffected by a physiologic preload, whereas the systolic strain might be altered by major changes in the preload [20]. The isovolumetric acceleration correlated well to invasive indices of intraventricular pressures and could be a superior measure of systolic performance, compared with other non-invasive methods [9].

In our study all included patients presented with nontreated OSA and morphological and functional parameters from M-mode and 2D transthoracic echocardiography within reference range. As exclusion criteria were applied arterial or pulmonary hypertension, as well as a known cardiovascular disease. In the main our patients did not suffer from any kind of respiratory disease, so they did not have a concomitant disease which might contribute to LV impairment. Our results for significant decrease of the assessed TDI parameters in OSA - LV end-systolic longitudinal strain, LV peak-systolic strain rate, isovolumetric acceleration of the septal and lateral mitral annulus confirmed: (1) the recently published data that myocardial systolic function of the left ventricle is often impaired in patients with OSA and (2) the opportunity these early changes in LV function to be correctly evaluated by TDI methods. All patients with OSA, involved into a study, will be followed-up for cardiovascular events occurrence, as well as for morbidity and mortality rate.

## Limitations

The limitations of our study are as follows: (1) The involved patients with OSA had a moderate obesity (mean BMI:  $31.4 \pm 3.2$  kg/m<sup>2</sup>), i.e. these ones with overweight and extreme obesity were not evaluated. In this setting our data might not be applicable to the whole OSA population; (2) The assessed OSA subjects were predominantly males (2/3) and our results could not be directly attributed to females, suffering from OSA; (3) This is a cross-sectional study with a relatively small number of OSA patients. They were with normal systolic and diastolic LV function by echocardiography and without known cardiovascular diseases, but additional investigations (stress-test, invasive assessment etc.) were not performed.

## Conclusion

Tissue Doppler Imaging might be a reliable method for detection of early abnormalities in LV function in patients with OSA. Reduction of longitudinal strain, strain rate and isovolumetric acceleration might be present in patients with OSA, even without overt diastolic or systolic LV dysfunction. Further studies with larger sample size are needed.

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