Overnight sleeping induced daily repetitive left ventricular systolic and diastolic dysfunction in obstructive sleep apnoea: quantitative assessment using tissue Doppler imaging

Nobuhiko Haruki1, Masaaki Takeuchi1*, Hiromi Nakai1, Yoshio Kanazawa2, Noriko Tsubota2, Rie Shintome2, Roberto M. Lang3, and Yutaka Otsuji1

1Second Department of Internal Medicine, University of Occupational and Environmental Health, School of Medicine, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan; 2Department of Cardiology, Tsukazaki Memorial Hospital, Himeji, Japan; and 3Noninvasive Cardiac Imaging Laboratory, University of Chicago Medical Center, Chicago, IL, USA

Received 18 February 2009; accepted after revision 9 May 2009; online publish-ahead-of-print 6 June 2009

Aims Although left ventricular (LV) diastolic dysfunction is frequently observed in patients with obstructive sleep apnoea (OSA), the effects of overnight sleeping on LV function remain unclear. The aim of this study was to determine acute effects of overnight sleeping on LV function in OSA patients.

Methods and results In 29 OSA patients with normal LVEF and 20 control subjects, tissue Doppler imaging (TDI), standard 2D, and Doppler echocardiography were acquired before and immediately after overnight sleep. Peak systolic (S'), early diastolic (E'), and late diastolic (A') annular velocities at septal and lateral corners were measured and averaged. The prevalence of hypertension was more often, LV mass index (102 ± 16 vs. 89 ± 18 g/m², P < 0.05) and left atrial volume index (25.3 ± 4.0 vs. 22.3 ± 4.4 mL/m², P < 0.05) were larger in OSA patients. Before sleeping, OSA patients had reduced E'/A ratio suggesting impaired relaxation. Although no significant differences in S' were noted between the two groups, E' was lower and A' was higher in OSA patients compared with control subjects. Compared with before sleeping, S', E', and A' were significantly reduced after overnight sleep in both groups, but the per cent reduction of S' and A' was significantly larger in OSA patients. A weak but significant correlation between per cent reduction of S'(A') and apnoea–hypopnoea index was noted.

Conclusion Overnight sleeping in OSA patients is associated with the development of subclinical systolic dysfunction and exaggerated diastolic dysfunction.

KEYWORDS
Obstructive sleep apnoea; Tissue Doppler imaging; Longitudinal function

Introduction
Obstructive sleep apnoea (OSA), which is characterized by repetitive apnoea or hypopnoea due to narrowing of the upper airways during sleep, is a common condition affecting ~5–15% of middle-aged population in western countries.1 Hypoxia and hypercapnia induced by repetitive obstructive apnoea adversely affect on myocardial oxygen demand and supply, resulting in the development of myocardial ischaemia and compensatory activation of sympathetic nervous system, which leads to an increase in left ventricular (LV) afterload and a decrease in LV preload.2 Several studies have demonstrated that OSA has an independent risk for cardiovascular morbidity and mortality.3,4

Although diastolic function is often impaired in OSA,5–7 OSA patients without other cardiovascular disease usually exhibit normal LV ejection fraction (LVEF). However, normal value of LVEF does not always guarantee normal LV systolic function. Radial shortening is predominantly dependent upon the contraction of circumferential myocardial fibres in the mid-wall, whereas longitudinal shortening is governed by both longitudinal subendocardial and subepicardial fibres. Since the subendocardium is more vulnerable to myocardial ischaemia, assessment of LV longitudinal function might be a sensitive marker for detecting subclinical alterations in LV systolic performance.8,9 Mitral annular velocity using tissue Doppler imaging (TDI) is a suitable
modality for the measurement of LV longitudinal function. We hypothesized that overnight sleeping might induce LV systolic and diastolic dysfunction in patients with OSA. Thus, the aim of this study was to determine the acute adverse impact of overnight sleeping on LV systolic and diastolic function in OSA patients using TDI.

Methods

Study design and patient population

From January 2007 to March 2007, we recruited 42 consecutive patients with newly diagnosed OSA (mean age: 47 ± 14 years) who had no following exclusion criteria in the Tsukazaki Memorial Hospital. Exclusion criteria were the following: (i) central sleep apnoea, (ii) history of coronary artery disease or electrocardiographic changes suggestive of myocardial infarction, (iii) obvious LV systolic dysfunction (LVEF < 50%) or a history of congestive heart failure, (iv) atrial fibrillation, (v) moderate to severe valvular diseases, (vi) hypertrophic cardiomyopathy, (vii) history of chronic obstructive pulmonary disease or asthma, (viii) previous diagnosis of OSA, and/or the previous use of continuous positive airway pressure therapy. All patients had been complained of daytime sleepiness and/or loud snoring. In addition, a total of 28 asymptomatic subjects (mean age: 33 ± 7 years) who did not have any typical symptoms with OSA were recruited as a control group. All patients and control subjects had undergone overnight polysomnography to determine the presence and severity of OSA. Complete transthoracic echocardiogram had been also performed before the sleep and immediately after the awake on the next morning. Because ageing significantly affects diastolic function, we selected patients in order to adjust age between the two groups. Thus, final group consisted of 29 OSA patients (mean age: 40 ± 8 years) and 20 control subjects (mean age: 36 ± 6 years, \( P = NS \)). The Ethics Committee of Tsukazaki Memorial Hospital approved the protocol, and all subjects gave written informed consent for the enrolment.

Sleep study

Overnight polysomnography was performed in the sleep laboratory using standard recording techniques (Sleep watcher E series, Compumedics, Abbotsville, Australia) and Profusion PSG. Surface electrodes were applied to perform electroencephalogram, chin electromyogram, electrocardiogram, and electrooculography. Airflow was monitored using an air pressure sensor placed at the nose and thermistor placed at the nose and mouth, and arterial oxygen saturation (\( \text{SaO}_2 \)) was recorded continuously with a pulse oximeter. Arousals were scored according to accepted definitions. \(^\text{10}\) Sleep was defined according to the criteria of Rechtschaffen and Kales. \(^\text{11}\) Apnoeas were defined as complete cessation of inspiratory airflow for at least 10 s. Hypopnoeas were defined as significant reduction (>50%) in respiratory signals for at least 10 s associated with an arousal or oxyhaemoglobin desaturation of 3% or more from baseline. The apnoea–hypopnoea index (AHI) was defined as the number of apnoeas and/or hypopnoeas events per hour of sleep. Patients with AHI of 5 or more were considered to have OSA. AHI < 5 was defined as normal.

Standard echocardiography

Echocardiography was performed in the left lateral decubitus position with a commercially available ultrasound machine (Vivid I, GE Healthcare, Milwaukee, WI, USA) and 3S-RS (3.5 MHz) probe. All images were obtained from standard parasternal and apical position using 2D, M-mode, and Doppler echocardiographic techniques. All examinations were performed by an experienced cardiologist who was unaware of the results of polysomnography. The LV end-diastolic and end-systolic dimensions, as well as interventricular septum and posterior wall thicknesses, were obtained from M-mode echocardiography. LV mass was determined by the Devereux\(^\text{12}\) formula, and corrected by body surface area yielding LV mass index (LVMi). LVEF was measured using biplane Simpson’s method according to the recommendation of American Society of Echocardiography. \(^\text{13}\) Left atrial volume (LAV) was assessed by the biplane area-length method from apical four- and two-chamber views. Measurements were obtained at end-systole from the frame preceding mitral valve opening, and the volume was indexed for body surface area. \(^\text{14}\) Pulse Doppler sample volume was placed at the mitral valve tips in the apical four-chamber view to record LV inflow velocity. From LV inflow velocity, early diastolic peak flow velocity (E), late diastolic peak flow velocity (A), E/A ratio, and deceleration time of the E wave velocity were measured. Isovolumic contraction and relaxation times were also calculated from LV inflow and outflow tract velocities. \(^\text{15}\)

Tissue Doppler echocardiography

Tissue Doppler echocardiography was recorded from the apical four-chamber view with the pulse-wave Doppler sample volume placed on the septal and lateral corners of the mitral annulus. Care was taken to ensure an ultrasound beam parallel to the direction of the mitral annular motion. Filters were set to exclude high-frequency signals, and gains were set to obtain clear tissue signals with minimal background noise. Peak systolic (S'), peak early (E'), and late (A') diastolic mitral septum and lateral annular velocities were measured, and these values were averaged. \(^\text{16}\)

Intra- and inter-observer variability

Intra-observer variability was determined by having an observer repeating the measurements of S', E', and A' in 20 randomly selected OSA patients or control subjects before and after sleeping 1 month apart. Inter-observer variability was determined by having a second observer to measure these variables in the same 20 patients or subjects. Intra- and inter-observer variability values were calculated as the absolute difference between the corresponding two measurements as a per cent of the mean.

Statistical analysis

Data were expressed as mean values ± SD. Frequencies were expressed as percentages. All statistical analysis was performed using statistical software (Statview, version 5.0 SAS Inc., NC, USA). Differences in continuous variables between the two groups were calculated using paired or unpaired \( t \)-tests. Categorical variables were compared using Fisher’s exact test or \( \chi^2 \) test whenever appropriate.
Linear regression analysis was used to investigate the relationship between two parameters. A $P$-value of $<0.05$ was considered to be significant.

**Results**

**Baseline findings**

Clinical characteristics of OSA patients and control subjects are shown in Table 1. Both groups were similar with regard to height, total cholesterol levels, low-density lipoprotein levels, brain natriuretic peptide levels, and the prevalence of diabetes mellitus. However, OSA patients had larger body weight and higher prevalence of hypertension and hyperlipidaemia compared with control subjects. The results of polysomnography are depicted in Table 2. For standard 2D echocardiographic measurements, LV internal diameter was not different between the two groups (LV end-diastolic diameter: $46.7 \pm 3.9$ vs. $46.6 \pm 3.7$ mm, LV end-systolic diameter: $29.0 \pm 4.2$ vs. $28.4 \pm 3.3$ mm, $P = NS$). However, LVM1 ($102 \pm 16$ vs. $89 \pm 18$ g/m$^2$, $P < 0.05$) and LAI (25.3 $\pm$ 4.0 vs. 22.3 $\pm$ 4.4 mL/m$^2$, $P < 0.05$) were significantly larger in OSA patients compared with control subjects.

**Haemodynamics and echocardiography before the sleeping**

Haemodynamics and echocardiographic variables between the two groups are shown in Table 3. Before sleeping, OSA patients had faster heart rate and higher systolic blood pressure compared with control subjects. The E/A ratio and E' were lower and A' was higher in OSA patients compared with control subjects. No significant difference of LVEF and S' was noted between the two groups. These findings suggested that OSA patients have already impaired diastolic function with preserved systolic function before the sleeping.

**Changes in haemodynamics and left ventricular function after overnight sleeping**

Heart rate and systolic blood pressure were decreased after the sleep in both groups (Table 3). LVEF was similar before and after the sleep in both groups. Although control subjects did not show any changes in E and A wave velocity after the sleep, A wave velocity was significantly reduced after the sleeping in OSA patients. All parameters of mitral annular velocity were decreased after the sleeping in both groups (Figure 1). However, per cent reduction of S' and A' during sleeping was significantly larger in OSA patients compared with control subjects (Figure 2).

**Relationship between left ventricular longitudinal function and severity of obstructive sleep apnoea**

AHI was significantly correlated with S' ($r = 0.42, P < 0.005$) and E' ($r = 0.51, P < 0.001$) obtained after the sleeping. No significant correlation was noted between AHI and A'. A significant but weak correlation was also noted between per cent reduction of S' during sleeping and AHI ($r = 0.43$,

### Table 1 Clinical characteristics of the study groups

<table>
<thead>
<tr>
<th></th>
<th>OSA (AHI $\geq$ 5) (n = 29)</th>
<th>Control (AHI $&lt; 5$) (n = 20)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40 $\pm$ 8</td>
<td>36 $\pm$ 6</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>29/0</td>
<td>19/1</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82 $\pm$ 14</td>
<td>70 $\pm$ 10</td>
<td>0.0012</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173 $\pm$ 6</td>
<td>173 $\pm$ 6</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>27.6 $\pm$ 4.3</td>
<td>23.4 $\pm$ 2.9</td>
<td>0.0004</td>
</tr>
<tr>
<td>Body surface area (m$^2$)</td>
<td>1.98 $\pm$ 0.18</td>
<td>1.83 $\pm$ 0.15</td>
<td>0.0032</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (31%)</td>
<td>1 (5%)</td>
<td>0.0263</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>22 (76%)</td>
<td>3 (15%)</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (10%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>9 (33%)</td>
<td>3 (15%)</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>202 $\pm$ 34</td>
<td>192 $\pm$ 20</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>121 $\pm$ 27</td>
<td>113 $\pm$ 21</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>44 $\pm$ 11</td>
<td>56 $\pm$ 17</td>
<td>0.0040</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>274 $\pm$ 136</td>
<td>157 $\pm$ 82</td>
<td>0.0013</td>
</tr>
<tr>
<td>Haemoglobin A1C (%)</td>
<td>5.3 $\pm$ 1.3</td>
<td>4.8 $\pm$ 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Brain natriuretic peptide (pg/mL)</td>
<td>8.9 $\pm$ 8.5</td>
<td>8.2 $\pm$ 5.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are presented as mean $\pm$ SD or absolute number (%).

LA, left atrial; LV, left ventricular.

### Table 2 Polysomnography data

<table>
<thead>
<tr>
<th></th>
<th>OSA (AHI $\geq$ 5) (n = 29)</th>
<th>Control (AHI $&lt; 5$) (n = 20)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnoea-hypopnoea index (/h)</td>
<td>34.7 $\pm$ 23.1</td>
<td>2.2 $\pm$ 1.4</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Apnoea index (/h)</td>
<td>19.0 $\pm$ 22.6</td>
<td>0.7 $\pm$ 0.6</td>
<td>0.0007</td>
</tr>
<tr>
<td>Hypopnoea index (/h)</td>
<td>15.9 $\pm$ 11.2</td>
<td>1.5 $\pm$ 1.1</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>396 $\pm$ 77</td>
<td>420 $\pm$ 55</td>
<td>NS</td>
</tr>
<tr>
<td>Lowest O2 saturation (%)</td>
<td>81 $\pm$ 9</td>
<td>91 $\pm$ 4</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>$&lt;90%$ saturation time (min)</td>
<td>23 $\pm$ 36</td>
<td>0.8 $\pm$ 3.1</td>
<td>0.0091</td>
</tr>
</tbody>
</table>

Data are presented as mean $\pm$ SD.
Although there was no correlation between percent reduction of E’ and AHI, a significant correlation was also noted between percent reduction of A’ and AHI (r = 0.47, P < 0.001). A significant but weak correlation was also noted between percent reduction of S’ (r = 0.29, P < 0.05) or A’ (r = 0.34, P < 0.05), and lowest O₂ saturation. There was no correlation between percent reduction of E’ and lowest O₂ saturation.

If we dichotomized OSA patients into mild and severe according to the AHI (mild: AHI < 30, n = 16; severe: AHI ≥ 30, n = 13), percent reduction of S’, E’, and A’ was significantly larger in the severe OSA group (Figure 3).

Among 29 OSA patients, two patients had taken cardiac medications including angiotensin receptor blockers in one and calcium antagonists in another patient. Even if we excluded these two patients into the analysis to obviate the impact of cardiac medication, the same results were obtained between the two groups.

Observer variabilities
Intra-observer variabilities for measuring S’, E’, and A’ were 5, 6, and 6%, respectively. Corresponding inter-observer variabilities were 8, 7, and 6.5%, respectively.
Major findings in this study were as following. Before the overnight sleeping: (i) impaired LV diastolic relaxation exhibiting lower E/A ratio and E', and higher A' were observed in OSA patients. (ii) However, no difference of LV longitudinal systolic function (S') and LVEF was noted between the two groups. After the sleep, (iii) no significant change of E and A wave velocity was noted in control subjects. However, A wave velocity was significantly lower in OSA patients. (iv) Both groups showed the reduction of S', E', and A' without any obvious change in LVEF. However, the per cent reduction of S' and A' was significantly larger in OSA patients compared with control subjects. (v) The per cent reduction of S' (A') was weakly but significantly correlated with AHI. To the best of our knowledge, this is a first study to demonstrate that overnight sleeping in OSA patients is associated with the development of subclinical systolic dysfunction and worsened pre-existing diastolic dysfunction using TDI.

**Diastolic function**

LV relaxation abnormality and the reduction of E' and augmentation of A' were observed in patients with OSA before the sleep. Several previous studies have been shown that OSA is frequently accompanied with diastolic dysfunction.5–7
However, patients with OSA often have coexisting disorders that prone to diastolic dysfunction such as ageing, obesity, hypertension, and diabetes. Thus, controversy exists whether OSA per se does independently impair LV diastolic function. We found significant correlation between AHI and E′ obtained after the sleep which was in agreement with the previous study. Kim et al. showed only E′ was identified as the best index to demonstrate an association between LV diastolic dysfunction and severity of OSA independently of body mass index, diabetes, and hypertension.

In this study, overnight sleeping produced further reduction of A velocity, E′, and A′ in OSA patients. Normally, sleep is accompanied by the reductions in central sympathetic tone, heart rate, blood pressure, and cardiac output. Burns et al. reported that decrease in heart rate is associated with the reduction of E velocity and E′ and augmentation of A velocity and A′. Recent study using parabolic flight clearly showed that S′, E′, and A′ are load-dependent, and decreased at preload reduction. Although change in loading condition and heart rate during overnight sleeping might produce the reduction of E′ and A′ even in normal subjects, the reduction of A wave velocity and exaggerated per cent reduction of A′ in OSA patients might be related to the repetitive hypoxia, because modest but significant correlation was noted between per cent reduction of A′ and AHI. The findings that per cent reduction of A′ was significantly larger in the severe OSA group (AHI ≥ 30) compared with the mild OSA group (AHI < 30, Figure 3) would further support this hypothesis. Thus, overnight sleeping makes pre-existing diastolic dysfunction become further exaggerated.

Systolic function

Controversy exists regarding LV systolic function in OSA. Some studies have addressed that OSA is accompanied with impaired LV systolic longitudinal function assessed by TDI. Although not statistically significant, it is interesting to note that S′ before the overnight sleeping is tended to be higher in OSA compared with control subjects in this study. This enhancement might be related to the compensatory increase in S′ due to higher heart rate by augmented sympathetic nervous tone. We also found that per cent reduction of S′ after sleeping is significantly larger in OSA compared with control subjects. OSA induced hypoxia, hypercapnia, and arousal from sleep may trigger sympathetic vasoconstrictor stimuli that raises systemic blood pressure and increases afterload. Acute increase in afterload can reduce LV systolic performance. Hypoxia itself can reduce LV systolic performance. Acute increase in afterload was noted between per cent reduction of E′ and A′ in control subjects before and after the sleep, though the degree was exaggerated in OSA patients. Although precise mechanisms are not known, AHI was not 0 even in control subjects in this study. Hypopnoea could produce the same adverse effects on LV function with mild degree in normal subjects. Reduction of preload during sleeping might be another mechanism for the reduction of S′, E′, and A′. The degree of intra- and inter-observer variability was nearly the same range of per cent reduction of E′ and A′ in control subjects. Thus, measurement variability could be partly contributed to these reductions. However, per cent reduction of S′ and A′ in OSA patients was much larger than observer variabilities. Thus, we think this was a real reduction during sleeping. Because TDI-derived measurements have angle-dependency, subtle change of angle of incidence might produce over- or under-estimate of the absolute value. Although OSA patients had severe degree of the disease, the real duration of the process was not known.

Limitations

Several limitations should be addressed in this study. Although this study was unique to determine the effect of overnight sleeping on LV longitudinal function, correlation between indices of LV longitudinal function and severity of OSA was modest. Because we could not manage timing from their last episode of hypoxia to recording of echocardiography after the awake on the next morning, some patients had enough time elapsed to recover from hypoxia-induced LV dysfunction. In addition, other confounding variables would affect these correlations. Although we adjusted age between the two groups, significant differences of prevalence of coronary risk factors and body mass index between the two groups make it hard to draw solid conclusions. Thus, this was a preliminary study of novel findings that are hypothesis-generating albeit not entirely definitive. There was corresponding directional change in S′, E′, and A′ in control subjects before and after the sleeping, although the degree was exaggerated in OSA patients. Although precise mechanisms are not known, AHI was not 0 even in control subjects in this study. Hypopnoea could produce the same adverse effects on LV function with mild degree in normal subjects. Reduction of preload during sleeping might be another mechanism for the reduction of S′, E′, and A′. The degree of intra- and inter-observer variability was nearly the same range of per cent reduction of E′ and A′ in control subjects. Thus, measurement variability could be partly contributed to these reductions. However, per cent reduction of S′ and A′ in OSA patients was much larger than observer variabilities. Thus, we think this was a real reduction during sleeping. Because TDI-derived measurements have angle-dependency, subtle change of angle of incidence might produce over- or under-estimate of the absolute value. Although OSA patients had severe degree of the disease, the real duration of the process was not known.

Conclusions

Although our results were preliminary, we conclude overnight sleeping in OSA patients is associated with not only the development of subclinical systolic dysfunction but also worsened pre-existing diastolic LV dysfunction, which can be assessed by TDI. Recent study demonstrated that TDI-derived E′ improved after 6 months of continuous positive airway pressure therapy. Further study is required to investigate whether continuous positive airway pressure could alleviate sleep-induced LV dysfunction in OSA patients.

Conflict of interest: none declared.

References

Overnight sleeping induced daily repetitive LV systolic and diastolic dysfunction