

Effects of olmesartan on blood pressure and insulin resistance in hypertensive patients with sleep-disordered breathing

Tomotaka Dohi · Koji Narui · Takatoshi Kasai · Hisashi Takaya · Ayako Inoshita · Kenichi Maeno · Satoshi Kasagi · Sugao Ishiwata · Minoru Ohno · Tetsu Yamaguchi · Shin-ichi Momomura

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Abstract The increased risk of cardiovascular morbidity and mortality among patients with sleep-disordered breathing (SDB) has been linked to arterial hypertension and insulin resistance. However, an effective antihypertensive agent for patients with SDB has not been identified. We investigated the effect of the angiotensin II subtype 1 receptor blocker olmesartan in hypertensive patients with SDB. This prospective, one-arm pilot study included 25 male patients with untreated SDB (mean age, 52.7 ± 11.4 years). We measured blood pressure, oxygen desaturation index (ODI), cardiac function using echocardiography, and insulin resistance using the homeostasis model assessment (HOMA) before and after 12 weeks of olmesartan therapy (mean dose, 17.6 ± 4.4 mg/day). Olmesartan significantly decreased systolic blood pressure (151.4 ± 8.0 vs 134.0 ± 7.4 mmHg; $P < 0.001$), diastolic blood pressure (93.4 ± 7.1 vs 83.9 ± 6.3 mmHg; $P < 0.001$), and HOMA index (3.7 ± 2.9 vs 2.8 ± 1.9 ; $P = 0.012$). Furthermore, left ventricular ejection fraction significantly increased at 12 weeks (68.1 ± 5.1 vs $71.6 \pm 5.4\%$; $P = 0.009$). However, body mass index (BMI) and degree of SDB did not change (BMI, 26.6 ± 4.0 vs 26.6 ± 4.2 kg/m², $P = 0.129$; 3% ODI, 29.5 ± 23.1 vs 28.2 ± 21.0 events/h, $P = 0.394$). Olmesartan significantly reduced blood

pressure and insulin resistance in hypertensive patients with SDB without changing BMI or SDB severity.

Keywords Antihypertensive therapy · Sleep-disordered breathing · Insulin resistance · Olmesartan

Introduction

Since the early 1980s, sleep-disordered breathing (SDB) and the related clinical syndrome of sleep apnea have been associated with hypertension [1–4]. In patients with SDB, respiratory event-related intermittent hypoxia may lead to overactivation of the sympathetic nervous system and renin-angiotensin system (RAS), and the subsequent development of sustained increases in blood pressure [5, 6]. Sleep-disordered breathing is also associated with an increased risk of insulin resistance, type 2 diabetes, metabolic syndrome, and cardiac function [7–9]. However, there is insufficient evidence to suggest that a specific class of antihypertensive drugs should be used to control hypertension in patients with SDB.

None of the current hypertension guidelines address the use of antihypertensive agents in the treatment of hypertensive patients with SDB [10]. One study showed that in patients with obstructive sleep apnea (OSA), beta-blockers reduced blood pressure significantly more than calcium antagonists, diuretics, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II subtype 1 receptors (ARB) [11]. By contrast, large-scale clinical trials have reported a significantly greater antihypertensive effect in hypertensive patients treated with an ARB compared with those taking beta-blockers [12, 13]. Because patients with SDB show enhanced RAS activity, drug therapy with RAS inhibitors might be useful in preventing subsequent organ

T. Dohi (✉) · S. Ishiwata · M. Ohno · T. Yamaguchi
Cardiovascular Center, Toranomon Hospital, 2-2-2 Toranomon,
Minato-ku, Tokyo 105-8470, Japan
e-mail: tomotakadohi@msh.biglobe.ne.jp

K. Narui · T. Kasai · H. Takaya · A. Inoshita · K. Maeno ·
S. Kasagi
Sleep Center, Toranomon Hospital, Tokyo, Japan

S. Momomura
Saitama Medical Center, Jichi Medical University,
Saitama, Japan

damage. Olmesartan, an ARB, has been shown to lead to significantly greater reductions in blood pressure than other ARBs; it also has anti-inflammatory effects and reduces insulin resistance [14–18]. We investigated the effect of treatment with olmesartan in hypertensive patients with untreated SDB.

Methods

Patients

Patients who attended an outpatient clinic in the Sleep Center at the Toranomon Hospital for evaluation of SDB were prospectively screened for the study. Hypertensive patients from the outpatient clinic who had SDB were included in the present study. Other inclusion criteria were as follows: hypertensive patients who had withdrawn from continuous positive airway pressure (CPAP) treatment or had difficulties continuing CPAP treatment in the outpatient clinic, or hypertensive patients who could not be hospitalized for polysomnography in our hospital for a long period. Exclusion criteria were previous or current cardiovascular disease, pulmonary disorders, diabetes mellitus, chronic renal failure, wall motion abnormalities as determined by echocardiography, and receiving ACE inhibitors or ARBs. Arterial hypertension was defined as mean systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg by mercury sphygmomanometer after at least 5 min of undisturbed rest in the sitting position, measured twice with an interval of 2 weeks. The assessment of disordered breathing during sleep was based on at least one overnight pulse oximetry. Informed consent was obtained from each patient. The protocol was approved by the institutional review board in our hospital, and the study was approved by the institutional ethics committee; all procedures were in accordance with institutional guidelines.

Study protocol

This was a prospective, single-center, before and after, pilot study. All patients were assigned to antihypertensive treatment with olmesartan for 12 weeks. Blood pressure was measured before and 4 and 12 weeks after treatment after a minimum of 5 min of undisturbed rest in the sitting position. For the purpose of consistency, conventional blood pressure measurements with mercury sphygmomanometers and appropriate cuff sizes were performed throughout the study. Blood pressure was measured in each patient by the same person at each visit. At least two measurements were made at each time point, and the mean values of these measurements were used. In

addition, body mass index (BMI) and waist circumference were measured in the outpatient clinic before and 12 weeks after treatment.

Patients initially received either 10 or 20 mg olmesartan daily; the higher dose was used if systolic blood pressure was >150 mmHg or diastolic blood pressure was >100 mmHg. After 4 weeks, if systolic blood pressure was >140 mmHg or diastolic blood pressure was >90 mmHg, we increased the dose of olmesartan to 20 mg if the patient was already receiving 10 mg olmesartan or added diuretics (2 mg trichlormethiazide daily) if the patient was already receiving 20 mg olmesartan. In addition, if systolic blood pressure was <110 mmHg after 4 weeks, the dose was halved to 10 mg olmesartan if the patient was receiving 20 mg olmesartan or 5 mg olmesartan if the patient was receiving 10 mg olmesartan.

Evaluation of sleep-disordered breathing

We diagnosed SDB using pulse oximetry during one night of sleep at home. Assessments were made using the oxygen desaturation index (ODI), which measures oxygen desaturation per hour. A 3% ODI was selected as an index of oxygen desaturation, representing the number of events per hour of recording time in which blood oxygen fell $\geq 3\%$. A 3% ODI threshold recorded during an estimated sleep duration of more than 4 h was used for the analysis. Because the duration of sleep estimated by pulse oximetry is often longer than the actual total sleep time, we had subjects fill out a sleep diary in order to exclude waking time from the analysis and thereby minimize potential overestimation of sleep duration. We defined significant SDB as 3% ODI levels greater than 15 events per hour [4]. Other usually derived indexes of arterial oxygen saturation (SaO_2), such as lowest SaO_2 and cumulative time spent below 90% SaO_2 , were also calculated before and after 12 weeks of treatment. The degree of sleepiness was assessed by the Epworth Sleepiness Scale (ESS) [19] before and after 12 weeks of treatment. The ESS is a simple questionnaire measuring the general level of daytime sleepiness.

Blood tests and echocardiography

Blood samples were obtained before and 12 weeks after treatment. Serum blood glucose, insulin levels, C-peptide levels, and lipid profiles (total cholesterol, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and triglycerides) were determined in the fasting state. The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as: $\text{HOMA-IR} = \text{fasting blood glucose} \times \text{insulin}/405$.

We evaluated cardiac function using standard echocardiography methods. To obtain the chamber quantification

using M-mode echocardiograms, the maximum minor axis of the left ventricle at end-diastole and end-systole was measured on the parasternal long-axis or short-axis view [20]. Left ventricular ejection fraction was calculated using the formula of Teichholz [21].

Statistical analysis

Continuous variables are expressed as mean \pm SD. To compare demographic and laboratory parameters before and after treatment, we used the Wilcoxon rank-sum test for continuous variables. Analysis of variance was used to compare changes in blood pressure from baseline to 4 and 12 weeks. Post hoc Tukey HSD tests were used to compare parameters within groups. A two-sided P value of less than 0.05 was considered significant. All data were analyzed using JMP version 7.0 for Windows (SAS Institute, Cary, NC, USA).

Results

We enrolled 25 male patients (mean age, 52.7 ± 11.4 years) from January 2008 to December 2008. Baseline and follow-up clinical characteristics are shown in Table 1. Six patients (24%) were receiving hepatic hydroxymethyl glutaryl-CoA reductase inhibitors, 3 (12%) were receiving aspirin, 2 (8%) were receiving diuretics, and 5 (20%) were receiving calcium channel blockers. These drugs and their dosages were maintained throughout the study.

Table 1 Clinical and laboratory characteristics of hypertensive patients with sleep-disordered breathing before and after 12 weeks of treatment with olmesartan

	Baseline	After 12 weeks	P value
BMI (kg/m^2)	26.6 ± 4.0	26.6 ± 4.2	0.129
Waist circumference (cm)	91.6 ± 10.0	93.7 ± 15.2	0.612
Glucose (mg/dL)	108.0 ± 19.7	102.0 ± 13.3	0.310
Insulin (mU/L)	14.0 ± 10.9	10.9 ± 7.6	0.004
HOMA-IR index	3.7 ± 2.9	2.8 ± 1.9	0.012
C peptide (ng/mL)	3.3 ± 1.9	2.6 ± 1.1	0.023
Glycated hemoglobin (%)	5.3 ± 0.6	5.3 ± 0.5	0.761
Total cholesterol (mg/dL)	208.8 ± 34.1	206.1 ± 38.0	0.263
LDL cholesterol (mg/dL)	126.7 ± 31.4	123.3 ± 31.1	0.186
HDL cholesterol (mg/dL)	47.1 ± 9.3	46.4 ± 8.0	0.723
Triglycerides (mg/dL)	164.6 ± 77.7	165.3 ± 84.5	0.639

Values are mean \pm SD. $P < 0.05$ was considered statistically significant
BMI body mass index, *HOMA-IR* homeostatic model assessment for insulin resistance, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein

Blood pressure and physical characteristics

Olmesartan treatment (17.6 ± 4.4 mg/day) resulted in a significant decrease of systolic and diastolic blood pressure after 4 weeks (systolic blood pressure, 151.3 ± 7.9 to 139 ± 6.7 mmHg; diastolic blood pressure, 93.3 ± 7.0 to 87.5 ± 5.6 mmHg, $P < 0.001$ vs baseline for both comparisons). At 4 weeks, 3 patients were increased from 10 to 20 mg olmesartan, and 2 patients at 20 mg olmesartan received diuretics. Consequently, blood pressure showed significantly greater reductions at 12 weeks compared with 4 weeks (systolic blood pressure, 134.2 ± 7.3 mmHg; diastolic blood pressure, 83.6 ± 6.3 mmHg; $P < 0.05$ for both comparisons) (Fig. 1). On the other hand, BMI and waist circumference were not significantly changed after 12 weeks of treatment (26.6 ± 4.0 vs 26.6 ± 4.2 kg/m^2 , $P = 0.129$; 91.6 ± 10.0 vs 93.7 ± 15.2 cm, respectively, $P = 0.612$). No patient had their dose of olmesartan halved during the study. In addition, no patient experienced adverse effects during the study, based on patient reports and blood tests performed at 4 and 12 weeks.

Blood tests

Insulin resistance improved after olmesartan treatment. HOMA-IR was decreased from 3.7 ± 2.9 at baseline to 2.8 ± 1.9 at 12 weeks ($P = 0.012$) (Fig. 2). There was a tendency for fasting blood glucose to decrease from baseline to 12 weeks, but differences were not significant (108.0 ± 19.7 vs 102.0 ± 13.3 mg/dL, $P = 0.310$). Insulin levels decreased significantly from baseline to end of treatment (14.0 ± 10.9 vs 10.9 ± 7.6 mU/L, $P = 0.004$). C-peptide levels also decreased significantly from baseline to 12 weeks (3.3 ± 1.9 vs 2.6 ± 1.1 ng/mL, $P = 0.023$). On the other hand, there were no significant changes in total cholesterol, HDL-C, LDL-C, or triglyceride levels over 12 weeks.

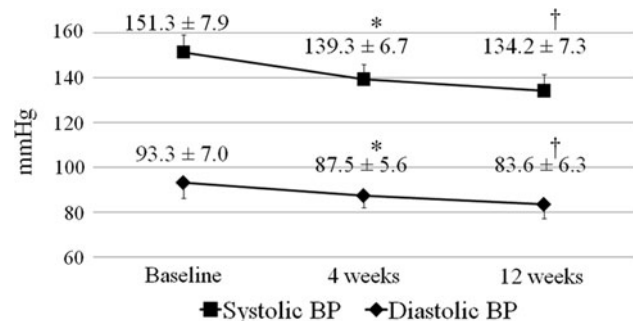


Fig. 1 Change in blood pressure (BP) over 12 weeks of olmesartan treatment. * $P < 0.05$ compared with baseline. † $P < 0.05$ compared with 4 weeks

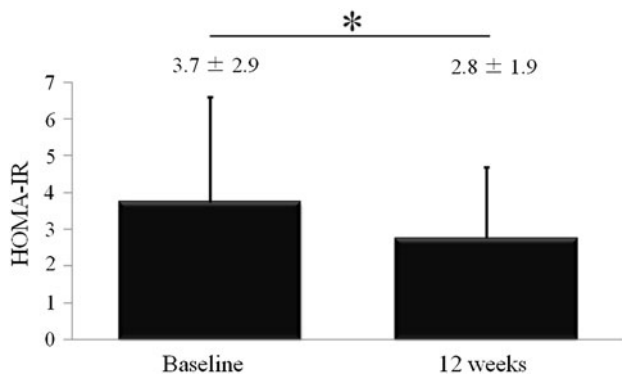


Fig. 2 Homeostasis model assessment for insulin resistance (*HOMA-IR*) before and after olmesartan treatment. * $P = 0.012$

SDB and cardiac function

There were no significant changes in the degree of SDB after olmesartan treatment (3% ODI, 29.5 ± 23.1 vs 28.2 ± 21.0 events/h, $P = 0.394$). Findings on pulse oximetry, including the lowest SaO_2 , percentage below 90%, and the ESS scores, did not change significantly. Results of echocardiography showed that systolic diameter was reduced after olmesartan treatment (30.3 ± 3.7 to 29.2 ± 3.8 mm, $P = 0.019$), whereas diastolic diameter was not significantly changed (49.3 ± 5.0 to 49.8 ± 5.0 mm, $P = 0.594$). Thus, ejection fraction was significantly increased after 12 weeks of treatment (68.1 ± 5.1 to $71.6 \pm 5.4\%$, $P = 0.009$) (Table 2).

Discussion

Olmesartan significantly reduced blood pressure and improved insulin resistance in hypertensive patients with SDB. We believe the present study provides important information that can be used in the management of hypertension in patients with SDB.

Large cross-sectional studies have shown a relationship between SDB and hypertension that is not explained by potential confounding by age, sex, or obesity [22, 23]. Therefore, it is important to consider the presence of SDB in the management of hypertension in clinical practice. Evidence of a link between SDB and hypertension is provided by clinical trials of nasal CPAP, showing that this treatment lowers blood pressure in these patients [24, 25]. However, despite the positive aspects of CPAP, compliance can be difficult to achieve, as this treatment can cause nasal congestion, claustrophobic sensations, and other side effects. Adequate compliance with CPAP is being increasingly recognized as a major determinant of treatment success [26]. Thus, hypertensive patients with SDB who do not tolerate CPAP will remain at high risk for

Table 2 Changes in sleep-disordered breathing and cardiac function before and after 12 weeks of treatment with olmesartan

	Baseline	After 12 weeks	<i>P</i> value
Pulse oximetry			
3% ODI (events/h)	29.5 ± 23.1	28.2 ± 21.0	0.394
Lowest SaO_2 (%)	74.5 ± 14.0	76.6 ± 12.9	0.840
% below 90%	11.1 ± 19.2	8.8 ± 15.9	0.923
ESS	9.7 ± 3.2	8.8 ± 1.9	0.414
Echocardiography			
LAD (mm)	36.3 ± 4.3	36.2 ± 3.3	0.603
AoD (mm)	33.1 ± 4.0	31.8 ± 3.0	0.061
Dd (mm)	49.3 ± 5.0	49.8 ± 5.0	0.594
Ds (mm)	30.3 ± 3.7	29.2 ± 3.8	0.019
EF (%)	68.1 ± 5.1	71.6 ± 5.4	0.009
IVS (mm)	9.5 ± 1.6	9.3 ± 1.1	0.478
PWT (mm)	9.7 ± 1.2	9.2 ± 1.1	0.034
DcT (ms)	236.9 ± 40.4	238.1 ± 51.2	0.933

Values are mean \pm SD. $P < 0.05$ was considered statistically significant. ODI oxygen desaturation index, SaO_2 arterial oxygen saturation, ESS Epworth sleepiness scale, LAD left atrial diameter, AoD aortic diameter, Dd diastolic diameter, Ds systolic diameter, EF ejection fraction, IVS intraventricular septal thickness, PWT posterior wall thickness, DcT deceleration time

cardiovascular disease [27]. We think such patients should be considered high risk, and be treated with adequate and intensive treatment for blood pressure control. This study shows that olmesartan decreases blood pressure in patients with hypertension and SDB.

The present study also demonstrated that olmesartan treatment for 12 weeks improved insulin resistance in middle-aged Japanese men. The association between SDB and abnormal glucose metabolism (insulin resistance) has been investigated in several studies [28, 29]. Although increased insulin resistance has also been shown to be related to obesity, in multiple analyses the association between OSA and insulin resistance was independent of obesity [30, 31]. Furthermore, in a large prospective cohort study in Japan, Muraki et al. [32] recently reported that intermittent nocturnal hypoxia episodes during the night are associated with an increased risk for type 2 diabetes, independent of traditional risk factors for diabetes. Thus, early treatment intervention for both SDB and insulin resistance may help reduce the risk of diabetes in hypertensive patients. In our study, HOMA-IR was improved by olmesartan, although no improvements in SDB and BMI were seen. De Vinuesa et al. [18] also reported that treatment with olmesartan improves glucose metabolism and insulin sensitivity and decreases some inflammatory parameters in patients with renal disease, hypertension, and metabolic syndrome. Our results support the antimetabolic

effects of olmesartan for hypertensive patients with SDB. It is not known whether this effect is shared by ARBs or is specific to olmesartan and independent of its angiotensin AT1 receptor-blocking activity [33]. In addition to changes in hemodynamic forces, additional mechanisms could be involved in the beneficial effects of olmesartan on insulin resistance because not all antihypertensive drugs improve insulin sensitivity [34]. In fact, diuretics and beta-blockers have been shown to worsen insulin sensitivity [35, 36]. In our results, insulin levels decreased significantly from baseline to 12 weeks. C-peptide is a pancreatic peptide of about 31 residues, depending on the species. Upon proteolytic cleavage of proinsulin, equimolar insulin and C-peptide are released. Therefore, we think the measurement of C-peptide is similar to the measurement of insulin. Measuring C-peptide in patients injecting insulin can help determine how much of their own natural insulin these patients are still producing. However, our study subjects did not include diabetic patients. Therefore, the changing levels of C-peptide might not have individual significance. In our results, there were similar changes in insulin and C-peptide levels before and after olmesartan treatment.

Moreover, it has been reported that patients with SDB have significantly higher levels of angiotensin II and aldosterone compared with healthy control subjects matched by body mass [37]. It is possible that the activation of the RAS is augmented by the presence of SDB and contributes to SDB-related hypertension. Therefore, we believe that olmesartan, an RAS inhibitor, is more effective than other classes of antihypertensive drugs for patients with hypertension and SDB. Pepin et al. [38] recently also reported the effect of ARB in hypertensive SDB patients in a randomized controlled trial. This report showed that valsartan, another ARB, induced a greater decrease in mean 24-h blood pressure than CPAP treatment, and the combination therapy of ARB and CPAP treatment was more effective. Thus, our results might further confirm the antihypertensive effects of an ARB in hypertensive SDB patients. We also consider RAS inhibition by olmesartan administration the effect of improvements in systemic vasoconstriction. As a result, we think afterload reduction induced by reduced systemic blood pressure influences the reduction of left ventricular wall stress. Moreover, this produces an increase in pump performance, as is seen from the effects on left ventricular systolic diameter and ejection fraction.

This study has several limitations. First, this was a small-scale, one-arm pilot study that included only 25 subjects. Large-scale, randomized controlled trials are needed to investigate the effects of olmesartan in comparison with other antihypertensive drugs. Second, we did not perform polysomnography to evaluate sleep quality. However, overnight pulse oximetry has been proposed as a simpler

alternative to polysomnography in the diagnosis of OSA because it is readily available, relatively inexpensive, and could potentially meet the large demand for diagnostic testing in the community [39, 40]. Pulse oximetry can be easily done at home and repeated if need be, which is not the case with polysomnography. Therefore, we believe that overnight pulse oximetry was useful enough to evaluate SDB in daily clinical practice, particularly for the management of hypertensive patients. Third, we did not evaluate changes in blood pressure using ambulatory blood pressure monitoring (ABPM). We thought about assessing blood pressure using ABPM, as this method is more accurate than simple monitoring in SDB patients. In fact, BP levels normally vary during different physiologic states and decline by 10%–20% at night during sleep compared with daytime during wakefulness. A nocturnal blood pressure decrease less than 10% of daytime blood pressure is defined as “nondipping.” Nondipping has been shown in patients with clinically symptomatic OSA, regardless of hypertension status. Therefore, we consider further study is necessary to investigate the antihypertensive effect of olmesartan using ABPM to estimate the clinical implications regarding hypertension and SDB.

In conclusion, olmesartan, an ARB, significantly reduced blood pressure and insulin resistance in hypertensive patients with SDB without changing BMI or SDB severity. These results might be useful for managing hypertensive patients with SDB who are resistant to or unable to tolerate CPAP therapy.

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Conflict of interest No author has any conflict of interest associated with this article.

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