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Metoprolol has a similar therapeutic effect as amlodipine on BP lowering in hypertensive patients with obstructive sleep apnea

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Abstracts

Purpose β-Blocker use has been controversial for a long time in the management of hypertensive patients with obstructive sleep apnea (OSA). The aim of present study was to compare the effects of metoprolol on BP lowering with amlodipine in hypertensive OSA patients.

Methods Hypertensive subjects with OSA were randomly assigned to metoprolol and amlodipine groups, receiving 12 weeks of oral either metoprolol (47.5 mg once daily) or amlodipine (5 mg once daily) treatment. At baseline and after the 12-week treatment period, 24-h ambulatory blood pressure monitoring was performed in both groups.

Results Both of metoprolol and amlodipine treatments significantly lowered 24-h blood pressure (BP) (from 143/88 to 132.3/81.6 mmHg; from 141.3/84.5 to 133.7/80.8 mmHg), daytime BP (from 146/90.2 to 136.4/84.6 mmHg; from 145.1/87.6 to 138.2/84.1 mmHg), and nighttime BP (from 139.1/83.9 to 125.7/76.2 mmHg; from 134.5/78.5 to 125.8/74.1 mmHg) (all $P < 0.05$). But there were no significant differences between the groups in BP variability ($P > 0.05$). Besides, metoprolol significantly reduced daytime heart rate (HR) ($P < 0.05$), while 24-h and nighttime HR values had no remarkable changes compared with baseline ($P > 0.05$).

Conclusions Metoprolol had similar therapeutic effects on BP lowering as amlodipine and could not decrease HR during the nighttime in hypertensive patients with OSA.

Keywords β_1-Blockers · Calcium channel blockers · Obstructive sleep apnea · Hypertension · Blood pressure

Introduction

Obstructive sleep apnea (OSA) is a highly prevalent chronic sleep disorder in middle-aged individuals that affects 3 to 7% and increases with age [1, 2]. It is characterized by recurrent collapse of the upper airway and sleep disruption, which could trigger a cascade of various pathophysiologic changes including endothelial dysfunction, increased sympathetic nervous system output, and overactivation of the renin-angiotensin system [3]. These processes may persist throughout the day in OSA patients and directly or indirectly lead to the incidence and development of hypertension, which in turn is able to cause or worsen OSA, thus maintaining a vicious circle between hypertension and OSA. Now, hypertensive and OSA patients have been identified as a special group of subjects, known to have an elevated prevalence of resistant hypertension and a higher risk of cardiovascular events, while lack effective, comfortable, and specific treatment.

Several recent studies evaluated the distinct effects of different antihypertensive drug classes on blood pressure variability (BPV) in hypertensive patients [4–6], and the data showed that calcium channel blockers may be the most efficient treatment in lowering BPV. The increased sympathetic tone in hypertensive patients with OSA suggests that a sympathetic antagonist might be an effective approach to lower blood pressure (BP) for the special group of subjects. In previous studies, we observed cardiac apoptosis, fibrosis, and sympathetic nerves hyperinnervation in the atrial, ventricular, lung, and aortic tissues of chronic OSA dogs [7–9], and

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metoprolol administration could significantly suppress structural and sympathetic remodeling above [10]. Based upon these findings, we speculate that β_1-blockers might be a good choice for antihypertensive treatment in OSA patients. However, the therapeutic effects of β_1-blockers and calcium channel blockers in hypertensive patients with OSA are still not very clear. Therefore, we performed this study to compare the potential effects of metoprolol and amlodipine on BP and HR in hypertensive patients with OSA.

Patients and methods

Study subjects

Never-treated adult subjects (age from 30 to 70 years) with hypertension and OSA (apnea-hypopnea index ≥ 5) were invited to participate in this prospective cohort study (ClinicalTrials.gov identifier: NCT02408172) between October 2013 and December 2014. We excluded individuals who had serious clinical events such as cerebrovascular disease, coronary artery disease, heart failure, or arrhythmia; individuals with serum creatinine more than 177 μmol/L, type 1 diabetes or uncontrolled type 2 diabetes (fasting blood glucose > 10 mmol/L), transaminase levels more than three times, symptomatic orthostatic hypotension, alcohol, or drug abusers; individuals with other suspected secondary hypertension and with pulmonary disease being treated with bronchodilators, corticosteroids, or oxygen; and pregnant women and individuals who are unable to perform the tests. A complete medical history and physical examination were conducted in all participants. Portable polysomnography was performed to establish the presence and the severity of OSA.

Study design

This was a randomized, controlled, parallel-group clinical trial. Subjects were randomized to receive 12 weeks of oral either metoprolol succinate sustained-release tablets (AstraZeneca, 47.5 mg once daily) or amlodipine (Pfizer, 5 mg once daily) treatment. Block randomization was done by using computer-generated random numbers. At baseline and after the 12-week treatment period, 24-h ambulatory BP monitoring was performed, and no continuous positive airway pressure was utilized during the BP monitoring nights in both groups.

Ambulatory blood pressure measurement

Twenty-four-hour ambulatory BP monitoring was executed using a fully automatic device (ABPM-05, Meditech Co. Budapest, Hungary) programmed to measure BP every 20 min from 6:00 AM to 10:00 PM and every 30 min from 10:00 PM to 6:00 AM. A proper cuff was selected according to the size of subject's arm and placed on the nondominant arm. Only subjects with at least 70% of valid measurements were included [11]. Cut-off values for the definition of hypertension for ambulatory BP monitoring were according to 2013 ESH/ESC Guidelines: daytime BP $\geq 135/85$ mmHg, nighttime BP $\geq 120/70$ mmHg, and/or 24-h BP $\geq 130/80$ mmHg [12].

According to the recordings, BPV was evaluated through the standard deviation (SD), coefficient of variation (CV), and average real variability (ARV) of the systolic and diastolic BP during daytime, nighttime, and over 24 h [13].

Polysomnography

Portable polysomnography (Acument7, Curative Medical Technology Inc., Suzhou, China) was designed to detect sleep apnea. The device has a position sensor, pressure transducer, and pulse oximeter. It was adjusted to the subject's chest using an effort belt to measure respiratory effort. Snoring and airflow were recorded by a nasal cannula. The oximeter and finger probes were used to measure oxygen saturation and pulse rate, respectively. The detection was performed at the subject's home during their usual sleep, mostly between 10:00 PM and 7:00 AM. Less than 6-h artifact-free recordings were excluded. Apneas were defined as cessation of airflow ≥ 10 s. Hypopnea was required to show more than a 50% decrement of airflow for 10 s or longer accompanied by at least 3% reduction in oxygen saturation. Apnea-hypopnea index was calculated as the numbers of apneas and hypopneas by the device. It was administered and analyzed by a registered technician.

Statistical analysis

Qualitative data were presented with count and percentile. Quantitative data were presented as mean ± SD or median. Student's t test/Wilcoxon rank sum test was used to compare the differences between the two groups. Paired data were analyzed by paired t test/Wilcoxon signed-rank test. Fisher's test was used to evaluate the qualitative data. Generalized linear models were used to evaluate multivariable effects with covariate adjusted. All statistical tests were two-tailed, and P values < 0.05 were considered statistically significant. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Inc.).

Results

Baseline clinical characteristics of the study participants

The trial design is shown in Fig. 1. Twenty hypertensive and OSA patients completed the present study. They were assigned to metoprolol ($n = 10$) and amlodipine ($n = 10$) groups. Demographics and baseline clinical characteristics are summarized in Table 1. There were no significant differences in age, gender, body mass index, apnea-hypopnea index, neck circumference, snoring history, nadir nocturnal oxygen saturation, and oxygen desaturation index between the two groups ($P > 0.05$).

Effects of amlodipine and metoprolol on systolic BP and BPV in hypertensive patients with OSA

Overall, BP changes were similar for all systolic BP parameters between the two treatment groups (Table 2). Both of metoprolol and amlodipine treatments significantly reduced 24-h mean systolic BP ($P = 0.0003$; $P = 0.0078$), daytime systolic BP ($P = 0.0098$; $P = 0.0357$), and nighttime systolic BP ($P = 0.0022$; $P = 0.0371$). Noticeably, there were no significant differences between the two treatments, not only in all systolic BP parameters but also in systolic BPV: the systolic BP SD of 24-h, daytime, and nighttime ($P = 0.1939$; $P = 0.2667$; $P = 0.2257$); the systolic BP CV of 24-h, daytime, and nighttime ($P = 0.0955$; $P = 0.0668$; $P = 0.2476$); 24-h systolic BP ARV ($P = 0.2685$). These data suggested that the effects of metoprolol and amlodipine on systolic BP and BPV were similar in hypertensive patients with OSA.

Effects of amlodipine and metoprolol on diastolic BP and BPV in hypertensive patients with OSA

As shown in Table 3, the effects of the two treatments on diastolic BP and BPV in hypertensive patients with OSA were also evaluated after adjustment for age, baseline diastolic BP, and HR after treatment. Consistently with the above systolic BP results, BP changes were also similar for all diastolic BP parameters between the two groups. Both of metoprolol and amlodipine treatments significantly reduced 24-h mean diastolic BP ($P = 0.0108$; $P = 0.0073$), daytime diastolic BP ($P = 0.0241$; $P = 0.0202$), and nighttime diastolic BP ($P = 0.0289$; $P = 0.021$). Besides, there were also no significant differences between the two treatments in diastolic BPV: the diastolic BP SD of 24-h, daytime, and nighttime ($P = 0.7779$; $P = 0.7853$; $P = 0.3838$); the diastolic BP CV of 24-h, daytime, and nighttime ($P = 0.9717$; $P = 0.525$; $P = 0.9793$); 24-

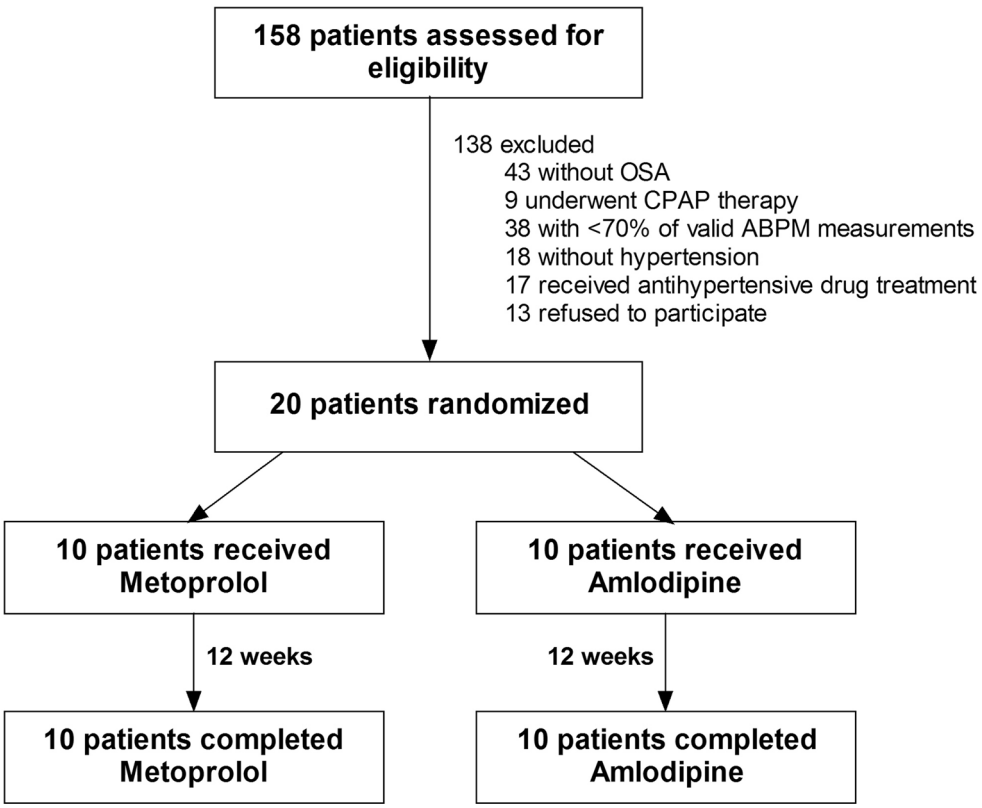

Figure 1 Flow chart. 158 subjects were assessed for eligibility, and 20 hypertensive patients with OSA were randomized to metoprolol (47.5 mg once daily, $n = 10$) and amlodipine (5 mg once daily, $n = 10$) groups. In total, 20 subjects completed the study. OSA, obstructive sleep apnea; CPAP continuous positive airway pressure; ABPM, 24-h ambulatory blood pressure monitoring

Table 1 Baseline patient characteristics

Variables	Amlodipine ($n = 10$)	Metoprolol ($n = 10$)	p
Age, year	50.10 ± 12.22	52.90 ± 6.91	0.5359
Sex, male (%)	8 (80%)	6 (60%)	0.6285
BMI, kg/m^2	28.66 ± 2.91	29.05 ± 2.16	0.7374
AHI, no./h	19.50	10.15	0.5966
Neck circumference, cm	42.00	40.00	0.7601
Snoring history, year	8.30 ± 2.21	7.90 ± 3.21	0.7495
Nadir nocturnal Sp_{O2}, %	61.50	80.00	0.2078
ODI, no./h	32.03 ± 18.33	29.66 ± 23.03	0.8019

Continuous variables were presented as means ± SD or median, compared by Student's *t* test or Wilcoxon rank sum test. Categorical variable was presented as no. (%), compared by Fisher's test. *BMI*, body mass index; *AHI*, apnea-hypopnea index; *ODI*, oxygen desaturation index

h diastolic BP ARV ($P = 0.4194$). These data demonstrated that the effects of metoprolol and amlodipine on diastolic BP and BPV were similar in hypertensive patients with OSA.

Effects of metoprolol and amlodipine on heart rate in hypertensive patients with OSA

As shown in Table 4, we observed the effects of two treatments on heart rate (HR) in hypertensive patients with OSA after adjustment for age, sex, and baseline HR. Amlodipine treatment had no significant effects on 24-h mean HR ($P = 0.5873$), daytime HR ($P = 0.9142$), and nighttime HR ($P = 0.2271$). On the other hand, metoprolol administration reduced daytime HR to 65.40 ± 15.41 ($P = 0.0437$, vs. baseline), but 24-h mean and nighttime HR values had no remarkable changes ($P = 0.0651$; $P = 0.4001$). These results indicated that metoprolol treatment could not decrease HR during nighttime in hypertensive patients with OSA.

Discussion

There are two novel and important findings in our study. First, metoprolol had similar therapeutic effects on BP lowering as amlodipine in hypertensive patients with OSA. Second, metoprolol treatment could not decrease HR during nighttime in hypertensive and OSA patients.

Hypertensive patients with OSA have been identified as a special group of subjects

During sleep, the breathing of an OSA sufferer is recognized as recurrent collapse of the upper airway and sleep disruption. This recurrent hypoxia condition leads to pathophysiologic changes including increased sympathetic activity and overactivation of the renin-angiotensin system [3]. It was reported that adrenergic activity was persistently increased in OSA patients during both wakefulness and sleep, and adrenergic tone might play a critical role in the development and

Table 2 Effects of amlodipine and metoprolol on systolic BP and BPV in hypertensive patients with OSA

Variables	Amlodipine		p*	Metoprolol		p*	p**
	Before	After		Before	After		
24-h SBP	141.30 ± 9.09	133.70 ± 8.63	0.0003	143.00 ± 17.04	132.30 ± 12.52	0.0078	0.1351
Daytime SBP	145.10 ± 9.50	138.20 ± 7.60	0.0098	146.00 ± 16.54	136.40 ± 10.86	0.0357	0.1835
Nighttime SBP	134.50 ± 10.39	125.80 ± 13.54	0.0022	139.10 ± 21.47	125.70 ± 17.24	0.0371	0.3875
24-h SBP-SD	15.50 ± 2.37	14.30 ± 2.16	0.1475	13.30 ± 2.79	14.30 ± 3.71	0.2126	0.1939
Daytime SBP-SD	14.90 ± 2.96	12.70 ± 2.63	0.0638	12.10 ± 2.77	12.80 ± 3.52	0.3901	0.2667
Nighttime SBP-SD	13.90 ± 3.87	12.1 ± 2.33	0.0744	13.20 ± 3.61	13.30 ± 3.65	0.9326	0.2257
24-h SBP-CV	0.11 ± 0.02	0.11 ± 0.02	0.4226	0.09 ± 0.02	0.11 ± 0.03	0.0762	0.0955
Daytime SBP-CV	0.10 ± 0.02	0.09 ± 0.02	0.1401	0.08 ± 0.02	0.10 ± 0.04	0.1086	0.0668
Nighttime SBP-CV	0.10 ± 0.03	0.10 ± 0.02	0.5505	0.10 ± 0.03	0.11 ± 0.03	0.3836	0.2476
SBP-ARV	13.04 ± 2.71	14.55 ± 7.85	1	12.56 ± 3.84	11.22 ± 2.41	0.3648	0.2685

Data are presented as means ± SD. p* were calculated with paired *t* test or Wilcoxon signed-rank test; p** were calculated with generalized linear models; the adjusted variables included age, baseline SBP, and heart rate after treatment. *BP*, blood pressure; *BPV*, blood pressure variability; *OSA*, obstructive sleep apnea; *SBP*, systolic blood pressure; *SD*, standard deviation; *CV*, coefficient of variation; *ARV*, average real variability

Table 3 Effects of amlodipine and metoprolol on diastolic BP and BPV in hypertensive patients with OSA

Variables	Amlodipine		p*	Metoprolol		p	p**
	Before	After		Before	After		
24-h DBP	84.50 ± 10.17	80.80 ± 11.14	0.0108	88.00 ± 9.30	81.60 ± 7.04	0.0073	0.4227
Daytime DBP	87.60 ± 11.38	84.10 ± 11.95	0.0241	90.20 ± 9.65	84.60 ± 5.83	0.0202	0.9319
Nighttime DBP	78.50 ± 8.59	74.10 ± 10.66	0.0289	83.90 ± 10.52	76.20 ± 10.06	0.021	0.5046
24-h DBP-SD	12.40 ± 2.95	10.70 ± 1.49	0.0635	9.20 ± 2.82	10.40 ± 1.96	0.2497	0.7779
Daytime DBP-SD	11.80 ± 3.46	9.80 ± 1.62	0.0711	8.50 ± 1.96	8.80 ± 1.75	0.7263	0.7853
Nighttime DBP-SD	10.90 ± 3.90	9.70 ± 1.83	0.4048	9.10 ± 5.09	10.40 ± 2.07	0.4372	0.3838
24-h DBP-CV	0.15 ± 0.04	0.13 ± 0.02	0.1973	0.11 ± 0.03	0.13 ± 0.03	0.0781	0.9717
Daytime DBP-CV	0.14 ± 0.05	0.12 ± 0.02	0.245	0.09 ± 0.02	0.11 ± 0.02	0.5273	0.525
Nighttime DBP-CV	0.14 ± 0.05	0.14 ± 0.03	0.8744	0.11 ± 0.06	0.14 ± 0.03	0.1727	0.9793
DBP-ARV	9.98 ± 1.82	10.14 ± 5.05	0.625	8.14 ± 1.82	8.21 ± 1.11	0.9144	0.4194

Data are presented as means ± SD. p* were calculated with paired t test; p** were calculated with generalized linear models; the adjusted variables included age, baseline DBP, and heart rate after treatment. *BP*, blood pressure; *BPV*, blood pressure variability; *OSA*, obstructive sleep apnea; *DBP*, diastolic blood pressure; *SD*, standard deviation; *CV*, coefficient of variation; *ARV*, average real variability

worsening of hypertension [3]. Our previous study found that sleep apnea could increase BPV, especially nighttime BPV [14]. BPV has considerable prognostic value for all-cause mortality and cardiovascular outcomes, independent of average BP [4, 15]. OSA-induced BPV increase may represent an explanation for OSA remaining "a major risk factor for cardiovascular diseases" [16]. So the optimal antihypertensive treatment strategy for hypertensive patients with OSA is increasingly urgent. Continuous positive airway pressure is currently the general care for moderate to severe OSA [17]. Recent evidence has proven that continuous positive airway pressure therapy could improve OSA symptoms, significantly decrease BPV, and reduce cardiovascular risk [18–20], while had a limited or no effect on clinic and ambulatory BPs in individuals with OSA [21, 22]. Otherwise, the disease severity, nasal resistance, and mood may influence the compliance of continuous positive airway pressure, and 46–83% of OSA patients are nonadherent to the treatment [23]. Therefore, patients with OSA have been identified as a special group of subjects, known to have an elevated prevalence of resistant hypertension and a higher risk of cardiovascular events, while lack effective, comfortable, and specific treatment.

The role of β-blockers in hypertensive patients with OSA is controversial

The increased sympathetic tone in hypertensive patients with OSA suggests that a sympathetic antagonist might be an effective approach to lower BP for the special group of subjects. But the application of β-blockers in the management of hypertensive OSA patients has been controversial for a long time. On the one hand, each sleep-disordered breathing episode in OSA patients could itself induce bradycardia and tachycardia, as well as frequent bradyarrhythmias [24–26], which might conceivably be potentiated by the negative chronotropic effects of β-blockers. Meanwhile, given that administration of non-selective β-blockers may evoke airway narrowing in OSA patients, β-blockers should not be plausibly applied to hypertensive patients with OSA. On the other hand, there are more and more evidences that a cardioselective β-blocker seems to be safe in patients with OSA in recent years [27]. A recent study showed that blockade of the excess sympathetic nervous activity with a β_1-blocker (nebivolol) could significantly lower both clinic and 24-h DBP in OSA subjects. More importantly, β_1-adrenergic receptor antagonist

Table 4 Effects of amlodipine and metoprolol on heart rate in hypertensive patients with OSA

Variables	Amlodipine		p*	Metoprolol		p*	p**
	Before	After		Before	After		
24-h HR, bpm	78.30 ± 11.73	77.00 ± 9.65	0.5873	72.60 ± 9.49	63.40 ± 13.45	0.0651	0.0311
Daytime HR, bpm	83.50 ± 12.01	83.80 ± 12.26	0.9142	77.40 ± 10.99	65.40 ± 15.41	0.0437	0.0128
Nighttime HR, bpm	70.00 ± 11.59	65.50 ± 8.75	0.2271	63.60 ± 8.78	60.40 ± 11.60	0.4001	0.5940

Data are presented as means ± SD. p* were calculated with paired t test; p** were calculated with generalized linear models; the adjusted variables included age, sex, and baseline heart rate. *OSA*, obstructive sleep apnea; *HR*, heart rate

could attenuate apnea-induced increases in HR while did not potentiate apnea-induced HR decelerations in patients with hypertension and untreated OSA [28]. Some studies examining the effects of cardioselective β_1-blockers have found no consistently deleterious effect on lung function either acutely or with long-term use [29, 30]. In previous studies, we observed cardiac apoptosis, fibrosis, and sympathetic nerves hyperinnervation in the atrial, ventricular, lung, and aortic tissues of chronic OSA dogs [7–9], and metoprolol administration could significantly suppress structural and sympathetic remodeling above [10]. Furthermore, the present results confirmed that metoprolol had similar therapeutic effects on BP lowering as amlodipine and could not decrease HR during the nighttime in hypertensive patients with OSA.

Limitation

In this study, sleep apnea was detected by portable polysomnography. This test could not exactly distinguish between obstructive and central sleep apneas, leading to some patients with central sleep apnea might be enrolled. The overall respiratory events may be also underestimated according to portable polysomnography features. Additionally, our study sample size was relatively modest, so the results need larger-scale research to confirm.

Conclusions We reported in detail that metoprolol had similar therapeutic effects on BP lowering as amlodipine and could not decrease HR during the nighttime in hypertensive patients with OSA. We expect the current study to provide valuable insights into the role of β_1-blockers as a new potential strategy for drug therapy in OSA-related hypertension.

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Compliance with ethical standards

The study was approved by the Ethics Committee of the First Affiliated Hospital of Harbin Medical University (ClinicalTrials.gov identifier: NCT02408172)

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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