Case Report

Sleep-Predominant Lowering of Ambulatory Blood Pressure by Bedtime Inhalation of a Novel Muscarinic M3 Receptor Antagonist: A New "Bronchoantihypertensive" Strategy Targeting the Lung in Hypertension with Chronic Obstructive Pulmonary Disease

Kazuomi KARIO[1)], Hideyuki UNO[2)], and Kazuyuki SHIMADA[1)]

Bedtime inhalation of a novel muscarinic M3 receptor antagonist markedly lowered ambulatory blood pressure (ABP), predominantly during sleep, in a chronic obstructive pulmonary disease (COPD) patient with masked nocturnal hypertension. This is the first case demonstrating that a bronchodilator significantly lowered ABP in a COPD patient with hypertension. This case suggests that bronchodilator therapy may have potential as a new antihypertensive strategy targeting the lung in hypertensive patients with impaired lung function. This "bronchoantihypertensive" therapy seems to be more effective for reducing sleep blood pressure in hypertensive patients with COPD and sleep hypoventilatory/hypoxemic syndromes. (*Hypertens Res* 2008; 31: 817–821)

***Key Words*: chronic obstructive pulmonary disease, nocturnal hypertension, a new "bronchoantihypertensive" strategy, muscarinic M3 receptor antagonist, lung function**

Introduction

Respiratory disorders have been reported to be associated with cardiovascular disease. Obstructive sleep apnea syndrome is well known to increase the risk of hypertension and cardiovascular diseases such as congestive heart failure, cardiac sudden death, myocardial infarction, and stroke. In addition, chronic obstructive pulmonary disease (COPD) has been recognized as a risk factor for cardiovascular disease. COPD and chronic heart failure (CHF) are common coexisting conditions, and the prevalence of COPD ranges from 20% to 30% in patients with CHF (*1*). COPD is a significant predictor of poor prognosis in patients with CHF (*2*) or post-myocardial infarction (*3*).

In addition, lung function is correlated with blood pressure (BP) in a healthy population. In a population-based cohort of middle-aged (55-year-old) men, lung function was inversely associated with a future BP increase (*4*). The BP increase between the ages of 55 and 68 years was highest among men who had low vital capacity (VC), and forced expiratory volume in 1 s (FEV_1) showed similar associations with BP change. The trends remained statistically significant after adjustment for smoking status. These findings indicate some pathophysiological linkage between the lungs and cardiovascular system.

We hypothesized that impaired lung function affects ambulatory BP (ABP) in COPD patients, and thus that improve-

From the [1)]Division of Cardiovascular Medicine, Jichi Medical University School of Medicine, Shimotsuke, Japan; and [2)]Division of Community and Family Medicine, Center for Community Medicine, Jichi Medical University School of Medicine, Shimotsuke, Japan.

Address for Reprints: Kazuomi Kario, M.D., Ph.D., Division of Cardiovascular Medicine, Jichi Medical University School of Medicine, Yakushiji 3311–1, Shimotsuke 329–0498, Japan. E-mail: kkario@jichi.ac.jp

Received August 29, 2007; Accepted in revised form November 1, 2007.

Table 1. Pulmonary Function before and during Inhalation of Tiotropium

	Baseline 2006/8/4	During tiotropium inhalation 2006/8/31	Change
VC (L)	1.80	2.26	+0.46
FVC (L)	1.71	2.12	+0.41
FEV_1 (L)	1.03	1.27	+0.24
IC (L)	0.87	1.08	+0.21
$\dot{V}_{50}$	0.64	0.88	+0.24
$\dot{V}_{25}$	0.28	0.24	−0.04

VC, vital capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; IC, inspiratory capacity; $\dot{V}_{50}$, maximal expiratory flow in 50% vital capacity; $\dot{V}_{25}$, maximal expiratory flow in 25% vital capacity.

Table 2. Twenty-Four-Hour Ambulatory Blood Pressure before and during Inhalation of Tiotropium

	Baseline 2006/8/1	During tiotropium inhalation 2006/8/31
Office BP (mmHg)	122/55	105/45
24 h BP (mmHg)	127/64	104/61
Awake BP (mmHg)	125/64	104/61
Sleep BP (mmHg)	131/64	104/61
Morning BP (mmHg)	134/74	106/56
Nocturnal BP reduction (%)	−5/0	0/0
Diurnal BP variation	Riser pattern	Non-dipper pattern
Office PR (/min)	74	54
24 h PR (/min)	55	55
Awake PR (/min)	56	56
Sleep PR (/min)	52	54
Morning PR (/min)	57	57
Time spent SpO_2<90% (%)	00:04:55 (1.06%)	00:02:15 (0.25%)

BP, blood pressure; PR, pulse pressure; SpO_2, saturation of oxygen.

ment of lung function would reduce ABP. To test this hypothesis, we investigated the effect of tiotropium (*5*), a novel muscarinic M3 receptor antagonist, on ABP in a COPD patient with hypertension.

Case Report

A 76-year-old man being treated for hypertension developed mild dyspnea on exertion. He was a smoker with a 5-year history of hypertension, and had been treated with an angiotensin receptor blockade (candesartan 8 mg per day) and a calcium channel blocker (cilnidipine 10 mg per day). The echocardiography revealed no abnormal findings indicative of hypertensive heart disease (left ventricular mass index: 116.8 g/m^2; left ventricular ejection fraction: 82%; E/A ratio of transmitral flow velocity: 1.35). A pulmonary function test revealed a VC of 1.8 L, forced VC (FVC) of 1.71 L, and FEV_1 of 1.03 L (65.2% of the predicted normal value), which was 60.2% of the forced VC, indicating moderate COPD (Table 1). Ambulatory BP monitoring revealed that awake BP (125/64 mmHg) was well controlled, but sleep BP (131/64 mmHg) was above the normal threshold (120/75 mmHg), indicating a riser pattern of nocturnal BP (Table 2, Fig. 1). A pulse oximeter worn simultaneously with the ABPM device revealed mild nocturnal hypoxia (time spent with saturation of oxygen <90%: 1.1%).

We tried inhalation of tiotropium (a novel M3 muscarinic receptor antagonist) at 18 μg/d without changing the other medications. One month after treatment, his pulmonary function was improved compared with baseline. The values of FVC, FEV_1, and inspiratory capacity (IC) were increased by 0.41 L, 0.24 L, and 0.21, respectively (Table 1).

One month after the beginning of the inhalation treatment, the 24 h BP level (127/64 mmHg→104/61 mmHg), particularly during sleep (131/64 mmHg→104/61 mmHg), was markedly decreased from the baseline ABPM (Table 2, Fig. 1). The dipping pattern was changed from a riser pattern at baseline to a nondipper pattern after treatment (nocturnal SBP dipping: 5% increase→0%). The pulse oximeter revealed that time spent with oxygen saturation <90% was improved from 1.1% to 0.25% after treatment. The patient noticed reductions in dyspnea associated with daily activities. In addition, even during the awake period when physical activity assessed by actigraphy was increased, ABP levels were lower than the baseline values.

Discussion

Bedtime inhalation of a novel muscarinic M3 receptor antagonist (*5*) markedly lowered ABP, predominantly during sleep, in a COPD patient with masked nocturnal hypertension. This is the first case demonstrating that a bronchodilator significantly lowered ABP in a COPD patient with hypertension. This case suggests that bronchodilator therapy may have potential as a new antihypertensive strategy targeting the lung in hypertensive patients with impaired lung function. This "bronchoantihypertensive" therapy seems to be more effective for reducing sleep BP in hypertensive patients with COPD and sleep hypoventilatory/hypoxemic syndromes (*6*).

Mechanism of Nocturnal Hypertension in COPD

COPD is a heterogeneous disorder characterized by dysfunction of the small and large airways, as well as by destruction of the lung parenchyma and vasculature, in highly variable combinations. Figure 2 summarizes the mechanism of the association between COPD and cardiovascular risk in relation to nocturnal hypertension (nondippers of nocturnal BP).

The major mechanism of nocturnal hypertension in COPD

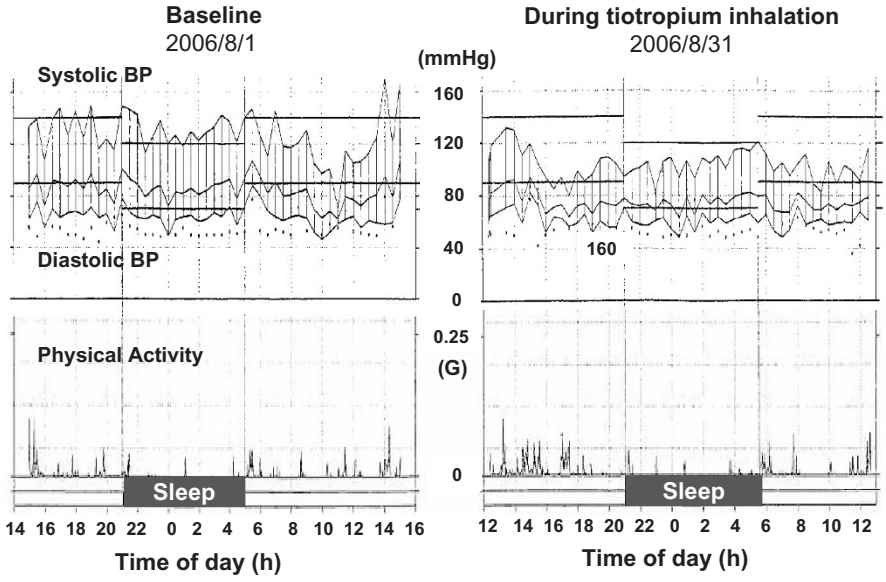

Fig. 1. *Twenty-four hour ambulatory blood pressure and physical activity before and during inhalation of tiotropium.*

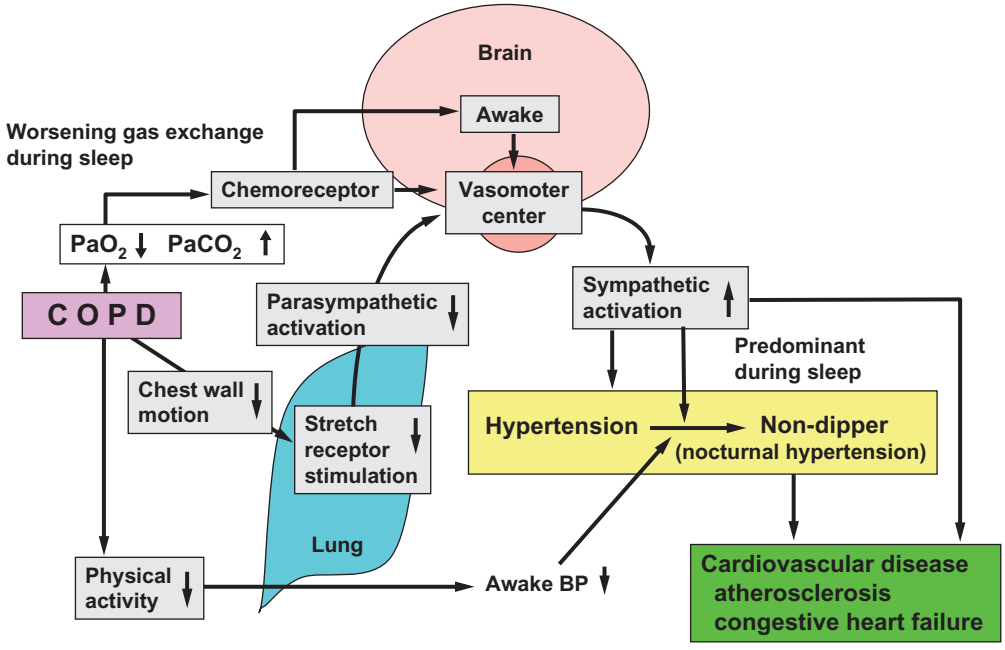

Fig. 2. *Mechanism underlying the association between chronic obstructive pulmonary disease (COPD) and cardiovascular risk.*

may be predominant activation of sympathetic nervous activation during sleep. COPD patients are reported to have increased sympathetic nervous system activation, as evidenced by their increased plasma norepinephrine levels (*7*). There is also direct evidence of increased sympathetic activation in patients with chronic respiratory failure. In patients with chronic respiratory failure including COPD, muscle sympathetic nerve activity (MSNA) as evaluated by microneurography of the peroneal nerve has been shown to be increased, and nasal oxygen administration reduces this increased sympathetic activation (*8*). This is partly explained by arterial chemoreflex activation and may play an important role in the pathogenesis of the disease.

Worsening Nocturnal Hypoxia

As shown in Fig. 1, hypoxia in this patient worsened significantly during sleep. This nocturnal hypoxia would activate sympathetic nervous system activity during sleep and lead to increased nocturnal BP and nondipper status in COPD patients. In addition, COPD is sometimes accompanied by worsening gas exchange during sleep, and is expressed as the phenotype of sleep-related hypoventilation/hypoxia syndrome, which is a new entity of sleep disorder (*6*). In this syndrome, abnormal gas exchange either worsens during sleep or may occur only at that time, due to altering control of breathing and/or pulmonary mechanics, which are affected by the sleep state, the sleeping posture, and the circadian rhythm driving sleep. These changes are largely inconsequential in the normal individual but interact with respiratory, neurologic, or neuromuscular diseases such as COPD to manifest as sleep-related hypoventilation/hypoxemic syndromes. Thus, COPD patients with coexistence of this syndrome may have increased sympathetic activation during sleep due to nocturnal hypoxia, which could lead to nocturnal hypertension and nondipping of nocturnal BP. The obstructive sleep apnea syndrome, which leads to development of nocturnal hypoxia due to frequent sleep apnea episodes, is known to be a risk factor for developing hypertension, particularly the nondipping type of nocturnal hypertension (*9–12*).

Reduced Physical Activity Masks Hypertension in COPD

Because of breathlessness and exercise intolerance, which are the most common COPD symptoms, physical activity during the daytime is going to decrease as the disease advances. As daytime ABP is closely determined by physical activity 5–10 min before ABP measurement (*13*), awake ABP is usually lower than expected in COPD patients with limited physical activity. Thus, in hypertensive patients with coexisting COPD, the progression of COPD would mask hypertension when BP control is assessed by clinic or self-measurement of BP. Thus, COPD may be likely to mask nocturnal hypertension.

Masked Nocturnal Hypertension in COPD

In a study of community-dwelling subjects with masked nocturnal hypertension, which was defined as a self-measured home BP level $<135/85$ mmHg and an ambulatory sleep BP level $\geq 120/75$ mmHg, the intima-media thickness and relative wall thickness of the left ventricle were found to be greater among masked nocturnal hypertensive patients than in the normotensive group (self-measured home BP level $<135/85$ mmHg and ambulatory nocturnal BP level $<120/75$ mmHg) (*14*). Rising or nondipping of nocturnal BP has been associated with the worst cardiovascular risk among various types of abnormal diurnal BP (*15–17*), even in normotensive subjects (*18*). Thus, strict and persistent ambulatory BP control throughout a 24 h period, including sleep BP control, is required in hypertensive patients, particularly in high-risk patients with other cardiovascular risks. In a cohort of patients with diagnosed and treated COPD, cardiovascular prognosis was closely associated with COPD severity (*19*). Thus, the 20% of patients with the highest COPD severity were 1.27 times more likely to have arrhythmia, 1.25 times more likely to have ischemic heart disease, 1.38 times more likely to have angina, 2.28 times more likely to have congestive heart failure, and 1.63 times more likely to die of cardiovascular disease than the 20% of patients with the lowest disease severity. Therefore, the masked nocturnal hypertension that develops as COPD becomes more severe should be adequately treated to achieve more effective prevention of these cardiovascular diseases.

Bedtime Tiotropium Inhalation

We here confirmed that bedtime tiotropium inhalation markedly lowered ABP, predominantly during sleep in a COPD patient with masked nocturnal hypertension. This new evidence was accompanied by improvement of nocturnal hypoxia. Tiotropium bromide is a quaternary ammonium compound structurally related to ipratropium, and was recently approved for treatment of COPD-associated bronchospasm (*5*). This anticholinergic bronchodilator's potency and long duration result primarily from a prolonged blockade of the M1 and M3 muscarinic receptors in the airways and a relatively more rapid dissociation from the M2 receptor (which provides inhibitory feedback). Multiple studies of a duration of up to 1 year have demonstrated its effectiveness as a bronchodilator for COPD, with a trough increase in FEV_1 of approximately 0.12 L and a peak increase of approximately 0.25 L. Tiotropium inhalation also leads to a significant reduction in static lung volumes in hyperinflated patients with COPD; this probably contributes to the reduction in dyspnea that is associated with long-term use of this maintenance bronchodilator.

Because a β-agonist bronchodilator may stimulate sympathetic nervous activity through β-adrenergic receptors, tiotropium, which is a non-β-agonist, would be more suitable for COPD patients with hypertension or cardiovascular disease. In a case report by Kato *et al*., this agent was effective for a COPD patient with congestive heart failure (*20*). In the present case report, we found that tiotropium had a marked sleep-predominant ABP-lowering effect in a hypertensive patient with COPD who had no hypertensive heart disease or CHF. We think one of the mechanisms that may explain the finding of Kato *et al*. (*20*) is that tiotropium controlled 24 h BP, including nocturnal BP. Nocturnal BP and a riser pattern of nocturnal BP are reported to be risks for CHF independently of clinic BP and the onset of myocardial infarction (*17*).

Perspectives

Based on the present findings, we are currently investigating the effectiveness of antihypertensive therapy targeting impaired lung function in hypertensives with respiratory disorders.

References

1. Le Jemtel TH, Padeletti M, Jelic S: Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol* 2007; **49**: 171–180.
2. Goldberg RJ, Ciampa J, Lessard D, Meyer TE, Spencer FA: Long-term survival after heart failure: a contemporary population-based perspective. *Arch Intern Med* 2007; **167**: 490–496.
3. Salisbury AC, Reid KJ, Spertus JA: Impact of chronic obstructive pulmonary disease on post-myocardial infarction outcomes. *Am J Cardiol* 2007; **99**: 636–641.
4. Engström G, Wollmer P, Valind S, Hedblad B, Janzon L: Blood pressure increase between 55 and 68 years of age is inversely related to lung function: longitudinal results from the cohort study 'Men born in 1914.' *J Hypertens* 2001; **19**: 1203–1208.
5. ZuWallack AR, ZuWallack RL: Tiotropium bromide, a new, once-daily inhaled anticholinergic bronchodilator for chronic-obstructive pulmonary disease. *Expert Opin Pharmacother* 2004; **5**: 1827–1835.
6. Casey KR, Cantillo KO, Brown LK: Sleep-related hypoventilation/hypoxemic syndromes. *Chest* 2007; **131**: 1936–1948.
7. Henriksen JH, Christensen NJ, Kok-Jensen A, Christiansen I: Increased plasma noradrenaline concentration in patients with chronic obstructive lung disease: relation to haemodynamics and blood gases. *Scand J Clin Lab Invest* 1980; **40**: 419–427.
8. Heindl S, Lehnert M, Criee CP, Hasenfuss G, Andreas S: Marked sympathetic activation in patients with chronic respiratory failure. *Am J Respir Crit Care Med* 2001; **164**: 597–601.
9. Bradley TD, Floras JS: Sleep apnea and heart failure: Part I: obstructive sleep apnea. *Circulation* 2003; **107**: 1671–1678.
10. Haas DC, Foster GL, Nieto FJ, *et al*: Age-dependent associations between sleep-disordered breathing and hypertension: importance of discriminating between systolic/diastolic hypertension and isolated systolic hypertension in the Sleep Heart Health Study. *Circulation* 2005; **111**: 614–621.
11. Shirasaki O, Yamashita S, Kawara S, *et al*: A new technique for detecting sleep apnea–related "midnight" surge of blood pressure. *Hypertens Res* 2006; **29**: 695–702.
12. Cui R, Tanigawa T, Sakurai S, Yamagishi K, Iso H: Relationships between sleep-disordered breathing and blood pressure and excessive daytime sleepiness among truck drivers. *Hypertens Res* 2006; **29**: 605–610.
13. Kario K, Schwartz JE, Pickering TG: Ambulatory physical activity as a determinant of diurnal blood pressure variation. *Hypertension* 1999; **34**: 685–691.
14. Hoshide S, Ishikawa J, Eguchi K, Ojima T, Shimada K, Kario K: Masked nocturnal hypertension and target organ damage in hypertensives with well controlled self-measured home blood pressure. *Hypertens Res* 2007; **30**: 143–149.
15. Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K: Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension* 2001; **38**: 852–857.
16. Kario K, Shimada K: Risers and extreme-dippers of nocturnal blood pressure in hypertension: antihypertensive strategy for nocturnal blood pressure. *Clin Exp Hypertens* 2004; **26**: 177–189.
17. Ingelsson E, Bjorklund-Bodegard K, Lind L, Arnlov J, Sundstrom J: Diurnal blood pressure pattern and risk of congestive heart failure. *JAMA* 2006; **295**: 2859–2866.
18. Hoshide S, Kario K, Hoshide Y, *et al*: Associations between nondipping of nocturnal blood pressure decrease and cardiovascular target organ damage in strictly selected community-dwelling normotensives. *Am J Hypertens* 2003; **16**: 434–438.
19. Curkendall SM, Lanes S, de Luise C, *et al*: Chronic obstructive pulmonary disease severity and cardiovascular outcomes. *Eur J Epidemiol* 2006; **21**: 803–813.
20. Kato M, Komamura K, Kitakaze M: Tiotropium, a novel muscarinic M3 receptor antagonist, improved symptoms of chronic obstructive pulmonary disease complicated by chronic heart failure. *Circ J* 2006; **70**: 1658–1660.