Case Report

Contribution of Cardiovascular Hypersensitivity to Orthostatic Hypertension and the Extreme Dipper Phenomenon

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We report the case of a 68-yr-old woman who, upon standing, experienced dizziness in association with increased blood pressure (BP) and heart rate (HR). We made a diagnosis of orthostatic hypertension and examined the BP response to postural change using the head-up tilt test. Positional change resulted in a 20-mmHg increase in systolic BP and a 15-bpm increase in HR. A 24-h ambulatory BP recording showed daytime hypertension that decreased at night, along with a nocturnal decrease in HR. Based on these post-diagnostic results, the patient was rediagnosed as an extreme dipper with silent lacunar infarction as the only complication of orthostatic hypertension. We suggest that, in our patient, the mechanism of orthostatic hypertension was hypersensitivity of cardiovascular responsiveness to endogenous vasoconstrictors. This was evidenced by increased pressure sensitivity to isoproterenol as well as phenylephrine. We thus selected carvedilol, a β -blocker with slight α -blocking action, and were more effective in abolishing the hypertension. (*Hypertens Res* 2000; 23: 119-123)

Key Words: orthostatic hypertension, extreme dipper, cardiovascular hypersensitivity

Introduction

In healthy individuals, changes in posture are accompanied by autoregulatory mechanisms that ensure relatively small fluctuations of blood pressure (1). Although orthostatic hypotension is well recognized and commonly encountered (2, 3), there have been few reports of orthostatic hypertension. Most of the cases of orthostatic hypertension that have been reported were related to excessive venous pooling with an initial drop in cardiac output followed by overcompensation with an excessive release of catecholamines (3-6), or to nephroptosis with orthostatic activation of the renin-angiotensin system (7, 8).

We here report the case of a 68-yr-old woman who, upon standing, experienced dizziness in association with increased blood pressure (BP) and heart rate (HR). To

determine the mechanism of orthostatic hypertension, we performed pharmacological tests of autonomic nervous system function and finally selected a more effective anti-hypertensive agent.

Case Report

A 68-yr-old woman was admitted to our hospital with high blood pressure (BP) and complaints of dizziness and shortness of breath. She provided the following history of her illness. She first experienced dizziness and a floating sensation approximately 20 yr earlier, at age 48.

She was first noted to have high blood pressure (BP) on a routine examination and was treated with amlodipine and captopril. At that time, she reported sometimes noticing a gradual onset of dizziness and shortness of breath. Upon admission to our hospital for further eval-

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Fig. 1. Head-up tilt test (pre-treatment). After the subject had been in the supine position for 15 min, the subject was then positioned upright on the tilt table at an angle of 60° using the foot board to bear the subject's weight. Head-up tilt test was continued for 15 min, after which the subject was returned to the supine position. The BP response to the positional change showed an initial drop from 139/78 mmHg to 131/77 mmHg, followed by an increase in systolic BP of 20 mmHg with an increase in HR from 78 bpm supine to 93 bpm on head-up condition.

uation, she provided the following history of her illness. She first experienced dizziness and a floating sensation approximately 20 yr earlier, at age 48. At that time, her family physician diagnosed her with high blood pressure. She was treated with nicardipine (20 mg), and her hypertension was moderately well controlled. At the age of 60, however, she again experienced dizziness and a floating sensation. Although she took some anti-hypertensive agents, such as angiotensin converting enzyme inhibitor, calcium antagonist, and β -blocker, her hypertension and symptoms were not improved. At the age of 50, she was also diagnosed with mild hypercholesteremia and hypothyroidism. Her hypertension, hypercholesteremia, hypothyroidism, and related symptoms continued to worsen until admission to our hospital. Upon admission, her BP and heart rate (HR) while supine were 137/69 mmHg and 78 beats per min (bpm), respectively, but upon standing, these increased to 170/69 mmHg and 95 bpm, and she complained of dizziness (Fig. 1). Laboratory tests, including tests of thyroid function and catecholamine levels, were normal (Table 1). Optic fundi were H₁S₁, Keith-Wagner I. Electrocardiogram results were normal. Chest radiography revealed normal cardiac size with a cardiothoracic ratio of 45%. Ultrasonic examination of the carotid artery showed no abnormalities. Magnetic resonance imaging of the brain demonstrated lacunar infarctions which did not appear to be associated with any of her symptoms.

We made a diagnosis of orthostatic hypertension and examined the BP response to postural change using the

Table 1. Laboratory Data on Admission

Hematology	
RBC	401 × 10 ⁴ /μl
Hb	10.9 g/dl
Ht	33 %
WBC	5,180 /μl
Plt	26.1 × 10 ⁴ /μl
Blood chemistry	
T.P.	7.3 g/dl
ALP	154 mU/ml
AST	10 mU/ml
ALT	6 mU/ml
LDH	261 mU/ml
CPK	47 mU/ml
BUN	14 mg/dl
Cr	0.5 mg/dl
Na	141 mEq/l
K	3.8 mEq/l
Cl	106 mEq/ml
T-Chol	180 mg/dl
TG	110 mg/dl
FBS	92 mg/dl
CRP	0.6 mg/dl
Endocrinology	
TSH	2.29 μU/ml
Free T4	1.3 μg/ml
Free T3	3.1 pg/ml
Anti-thyroglobulin Ab	>100
Anti-microsome Ab	8
Urinalysis	
Protein	(-)
Glucose	(-)
Ccr	75.5 ml/min

Table 2. Hemodynamic and Endocrine Responses to Head-Up Tilt Test

	Pre	Post
Systolic blood pressure (mmHg)	131	152
Diastolic blood pressure (mmHg)	77	84
Heart rate (bpm)	78	93
Adrenalin (ng/ml)	0.06	0.18
Noradrenalin (ng/ml)	0.36	0.49
Total catecholamine (ng/ml)	0.42	0.47
Renin (ng/ml/h)	0.5	0.7
Aldosterone (ng/dl)	7.7	9.4

head-up tilt test. The BP response to the positional change showed an initial drop from 139/78 mmHg to 131/77 mmHg, followed by an increase in systolic BP of 20 mmHg with an increase in HR from 78 bpm supine to 93 bpm on head-up condition. Venous plasma catecholamine and renin levels were within the normal range and

Fig. 2. A 24-h ambulatory BP recording showed daytime hypertension and a nocturnal fall with decreased heart rate at nighttime. Blood pressure and heart rate were measured every 30 min. Bar graph show average values of blood pressure and heart rate. Day time: 7:00 to 21:00, Night time: 21:00 to 7:00. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: heart rate.

demonstrated an appropriate increase when the patient was standing (Table 2).

To determine whether the patient had increased responsiveness to catecholamines, we examined two pressure responses, *i.e.*, the α -adrenergic responsiveness to norepinephrine and phenylephrine and the β -adrenergic responsiveness to isoproterenol, with the patient in the supine position. First, norepinephrine was infused at rates of 10, 25, 50, 75, 100, and 125 ng/kg per min for 10 min each. The pressure dose of norepinephrine required to raise the patient's systolic BP by 20 mmHg was 125 ng/kg per min, whereas in healthy subjects the required dose is 140 ng/kg per min and in hypertensive subjects the dose is 87 ng/kg per min (9, 10). Thus, the pressure sensitivity to norepinephrine was within the normal range. The pressure sensitivity to phenylephrine, defined as change in systolic BP per 100 μ g of drug, was 70 mmHg, which is a 4-fold increase over that in normotensive subjects (17 mmHg) and a 2-fold increase over that in hypertensive subjects (36 mmHg) (11). Second, β -adrenergic responsiveness was studied by rapid intravenous injections of 0.1, 0.2, 0.4, and 0.6 μ g isoproterenol and expressed as the dose required to increase HR by 25 bpm. Isoproterenol sensitivity was 0.6 μ g, *i.e.*, an approximately 3-fold increase in heart rate sensitivity to isoproterenol compared to that previously reported (12). Finally, angiotensin II (Ang II) was infused at rates of 0.2, 0.5, 1.0, and 2.0 ng/kg per min for 6 min each. The pressor dose, calculated as the amount of Ang II required to produce an increase in diastolic BP of 20 mmHg, was 6 ng/kg per min, which is within the normal range (13, 14). These infusion studies suggested that the patient had increased re-

Fig. 3. Head-up tilt test (after an α -blocker, doxazosin 2 mg/d treatment for 1 wk). Orthostatic hypertension was improved. However, this patient complaint for dizziness and palpitation with increased heart rate.

Fig. 4. Head-up tilt test (after a β -blocker, carvedilol 10 mg/d treatment for 1 wk). Orthostatic hypertension and tachycardia were improved.

sponsiveness to catecholamines, especially β -adrenergic responsiveness.

For further evaluation of BP, a 24-h ambulatory BP recording was made from the left upper arm. The patient had received no antihypertensive agents in the two weeks prior to the test. The results indicated daytime hypertension that decreased at night along with a nocturnal decrease in HR (Fig. 2).

A number of therapeutic agents were administered for 1 wk, and an α -blocker (doxazosin, 2 mg) was found to be effective for the postural hypertensive response but not for the chief complaints of dizziness and palpitation with increased HR (Fig. 3). Notably, carvedilol, a β -blocker with slight α -blocking action, at a dose of 10 mg was effective in abolishing postural hypertension and tachycardia (Fig. 4), as well as daytime hypertension (as measured

Post-treatment (carvedilol 10mg)

Fig. 5. A 24-h ambulatory BP recording after treatment with carvedilol showed improvements of daytime hypertension. Blood pressure and heart rate were measured every 30 min. Bar graph show average values of blood pressure and heart rate. Day time: 7:00 to 21:00, Night time: 21:00 to 7:00. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: heart rate.

by 24-h ambulatory blood pressure recording) (Fig. 5).

Discussion

We reported the case of a 68-yr-old woman with orthostatic hypertension and daytime hypertension. Previously, there has been one report of marked orthostatic hypertension that seemed to be mediated by vascular hypersensitivity to sympathetic activation (4). In this previous case, the patient had normal catecholamine levels and increased α but not β -sensitivity, and BP could be lowered by any vasodilator but was particularly sensitive to minute doses of α -blockers. In the present case, we speculate that the mechanism of orthostatic hypertension was hypersensitivity of cardiovascular responsiveness to endogenous vasoconstrictors. Our patient showed hypersensitivity to both α and β adrenoreceptor stimulants, as evidenced by increased pressure sensitivity to isoproterenol as well as phenylephrine. The mechanism responsible for the dissociation between the pressor responses to noradrenaline and phenylephrine has not been described in detail. However, functional or morphological differences between α_1 and α_2 adrenoreceptor might exist. We thus selected carvedilol, a β -blocker with slight α -blocking action, and were more effective in abolishing the hypertension.

Our patient showed a nocturnal fall in systolic BP and HR on ambulatory blood pressure recording. In a study by Kario *et al.* (15), subjects whose ambulatory blood pressure recordings showed a nocturnal decrease in systolic BP also showed disturbance of the autonomic nervous system—i.e., upregulation of sympathetic tone in the daytime—as well as advanced silent cerebrovascular dam-

age as a complication of hypertension. In the present case, our patient was diagnosed as an extreme dipper as defined in a report by Kario *et al.* (15), and had only silent lacunar infarction as a complication of hypertension. During ambulatory BP monitoring, BP measurements may be done several times during the daytime in the upright position. In ambulatory BP monitoring, BP measurements are generally made several times a day with the patient in an upright position, and these standing measurements probably contribute to increased waking BP levels in extreme dippers.

Recently, Kario *et al.* (16) also reported that extreme dippers showed a marked orthostatic BP rise in the upright position with head-up tilting, and that orthostatic hypertension was a risk factor for cerebral infarction. However, in their study there were no significant differences among extreme dippers, dippers, and non-dippers in the degree of HR rise, indicating that the extreme dipper phenomenon is due to hypersensitivity of vascular sympathetic activation. Interestingly, the present case demonstrated hypersensitivity not only of vascular sympathetic activation but also of cardiac sympathetic activation.

In conclusion, we here reported a case of orthostatic hypertension in association with the extreme dipper phenomenon, with the latter seemingly mediated by hyper-responsiveness to sympathetic activation. Carvedilol was effective in abolishing postural hypertension and daytime hypertension on 24-h ambulatory blood pressure recording. This case underscores the importance of the extreme dipper phenomenon, which can easily be missed if BP is measured only with the patient in a sitting position.

References

1. Currens JH: A comparison of the blood pressure in the lying and standing positions: a study in five hundred men and five hundred women. *Am Heart J* 1948; **35**: 646-654.
2. Hollister AS: Orthostatic hypotension; causes, evaluation and management. *West J Med* 1992; **157**: 652-657.
3. Kaplan NM: Two faces of sympathetic nervous activity: hypotension and hypertension. *Am J Med Sci* 1992; **303**: 271-279.
4. Benowitz NL, Zevin S, Carlsen S, Wright J, Schambelan M, Cheitlin M: Orthostatic hypertension due to vascular adrenergic hypersensitivity. *Hypertension* 1996; **28**: 42-46.
5. Streeten DHP, Auchincloss JH, Anderson GH, Richardson RL, Thomas FD, Miller JW: Orthostatic hypertension; pathogenic studies. *Hypertension* 1985; **7**: 196-203.
6. Sapru RP, Sleight P, Anand IS, Sambhi MP, Lopez R, Chhuttani PN: Orthostatic hypertension. *Am J Med* 1979; **66**: 177-182.
7. Tsukamoto Y, Komuro Y, Akutsu F, *et al*: Orthostatic hypertension due to coexistence of renal fibromuscular

- dysplasia and nephroptosis. *Jpn Circ J* 1988; **52**: 1408-1414.
8. Takada Y, Shimizu H, Kazatani Y, Azechi H, Hiwada K, Kokubu T: Orthostatic hypertension with nephroptosis and aortic disease. *Arch Intern Med* 1984; **144**: 152-154.
 9. Meier A, Weidmann P, Grimm M, et al: Pressure factors and cardiovascular pressure responsiveness in borderline hypertension. *Hypertension* 1981; **3**: 367-372.
 10. Ensinger H, Stein B, Jager O, Grunert A, Ahnefeld FW: Relationship between infusion rates, plasma concentrations, and cardiovascular and metabolic effects during the infusion of norepinephrine in healthy volunteers. *Crit Care Med* 1992; **20**: 1250-1256.
 11. Goldstein DS: Arterial baroreflex sensitivity, plasma catecholamines, and pressure responsiveness in essential hypertension. *Circulation* 1983; **68**: 234-240.
 12. Cleaveland CR, Rangno RE, Shand DG: A standardized isoproterenol sensitivity test. *Arch Intern Med* 1972; **130**: 47-52.
 13. Kaplan NM, Silah JG: The effect of angiotensin II on the blood pressure in humans with hypertensive disease. *J Clin Invest* 1964; **43**: 659-669.
 14. Bianchetti MG, Bereta-Piccoli C, Weidmann P, Ferrier C: Blood pressure control in normotensive members of hypertensive families. *Kidney Int* 1986; **29**: 882-888.
 15. Kario K, Matsuo T, Kobayashi H, Imiya M, Matsuo M, Shimada K: Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients: advanced silent cerebrovascular damage in extreme dipper. *Hypertension* 1996; **27**: 130-135.
 16. Kario K, Eguchi K, Nakagawa Y, Motai K, Shimada K: Relationship between extreme dippers and orthostatic hypertension in elderly hypertensive patients. *Hypertension* 1998; **31**: 77-82.