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RAPID COMMUNICATION

Diminished Circadian Blood Pressure Rhythm in Patients with Asymptomatic Normotensive Pheochromocytoma

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Summary

In our study, the circadian blood pressure (BP) rhythm was studied in subjects with asymptomatic and normotensive pheochromocytoma. We have therefore performed 24-hour BP monitoring not only in 6 subjects with asymptomatic pheochromocytoma, but also in 33 patients with symptomatic pheochromocytoma and in 10 normotensive subjects, who served as a control group. Circadian BP rhythm was expressed by assessing a relative night-time BP decline. We found a similar BP rhythm, catecholamine excretion and tumor size in subjects with both forms of pheochromocytoma. Subjects with asymptomatic pheochromocytoma had a significantly lower night-time systolic BP decline (P=0.01) and diastolic BP decline (P=0.006) than normotensive controls. We conclude that the attenuated night-time BP decline in normotensive and asymptomatic subjects with pheochromocytoma might be a possible sign of partial desensitization of the cardiovascular system to catecholamines.

Key words

Pheochromocytoma • Circadian blood pressure rhythm

Pheochromocytoma, a tumor arising from chromaffine cells, is a challenging diagnostic problem because it covers a very broad clinical spectrum – from being completely symptom-free to a variety of pheochromocytoma-related symptoms (sustained or paroxysmal hypertension, orthostatic hypotension, palpitations, headache, sweating etc.) (Bravo 1994, Mannelli *et al.* 1999, Kudva *et al.* 1999).

Hypertension, one of the most typical signs of pheochromocytoma, is characterized by mitigated circadian blood pressure (BP) variations as a possible sign of elevated sympathetic tone (Spieker *et al.* 1993, Middeke and Schrader 1994). In our study, the pattern of the diurnal BP rhythm of subjects with asymptomatic normotensive pheochromocytoma in comparison with symptomatic patients was investigated.

Thirty-nine subjects with a histologically proven pheochromocytoma were investigated at our department in the course of hospitalization between 1992-1999. Among these 39 subjects with pheochromocytoma six completely asymptomatic patients were identified. The remaining patients exhibited either typical paroxysmal symptoms with episodical hypertension or had at least treated mild arterial hypertension. The group of subjects with asymptomatic pheochromocytoma did not differ from the remaining subjects with pheochromocytoma in

baseline demographics, hormonal profile or tumor size (Table 1). Diagnosis of pheochromocytoma was established by analyzing a one-day sample of urinary free catecholamines (when necessary with metanephrines and normetanephrines) by means of fluorimetry or high performance liquid chromatography. Tumors were localized mostly by computed tomography.

24-hour ambulatory BP monitoring (Spacelabs 90207, SpaceLabs Medical, Richmond, USA) was performed during the day-time (from 06:00 h to 22:00 h) every 20 min and during the night-time (from 22:00 h to 06:00 h) every 30 min in order to obtain the circadian BP profile. The diurnal BP variation was characterized by the relative night-time BP decline calculated as follows

(day-time BP – night-time BP)/day-time BP x 100 %

Ten normotensive controls, who were studied at our department under the same conditions, served as a control group.

Table 1. Demographic and clinical characteristics of subjects with asymptomatic or symptomatic pheochromocytoma compared with a control group

Characteristics	**Asymptomatic pheochromocytoma**	**Symptomatic pheochromocytoma**	**Control group**
No. of subjects	6	33	9
Males/Females	4/2	14/19	3/6
Age (years)	36.9±9.9	46.4±13.9	43.2±11.7
BMI ($kg.m^{-2}$)	23.2±4.5	24.3±4.9	24.2±4.4
24-hour urinary epinephrine	7.8±1.6	12.3±2.2	n.a.
24-hour urinary norepinephrine	4.7±4.5	10.0±11.1	n.a.
24-hour urinary dopamine	0.8±1.0	1.6±4.4	n.a.
Tumor size (mm)	73±27	56±22	n.a.

Catecholamine values are expressed as a multiple of upper limits of normal range of two different methods (fluorimetry and high performance liquid chromatography) used at our department between 1992-1999. n.a., not available.

Table 2. Blood pressure and heart rate and its night-time decline in subjects with asymptomatic, symptomatic pheochromocytoma and control group.

Characteristics	**Asymptomatic pheochromocytoma**	**Symptomatic pheochromocytoma**	**Control group**
Office SBP (mmHg)	128±15	140±26	133±18
Office DBP (mmHg)	85±10	91±17	85±12
24-hour SBP (mm Hg)	128±9*	135±18	114±9
24-hour DBP (mm Hg)	82±4¶	85±13	73±6
24-hour HR (beats/min)	83±8	77±10	73±12
Relative night-time SBP decrease (%)	3±4¶	0±11	15±7
Relative night-time DBP decrease (%)	4±5¶	3±11	20±9
Relative night-time HR decrease (%)	15±8	12±12	18±9

*SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BP ± S.D. *$P<0.05$, ¶$P<0.01$ asymptomatic pheochromocytoma vs. control group.*

The data are shown as means ± S.D. The Mann-Whitney test was used for comparisons of continuous variables between the studied groups and the Fisher test also served for comparison of categorical variables. $P<0.05$ values were considered significant.

As expected, patients with symptomatic pheochromocytoma had higher BP values compared to the asymptomatic subjects (Table 2). These differences, however, did not reach a statistical significance. Similarly, we did not find any significant differences in the night-time BP decrease between symptomatic and asymptomatic pheochromocytoma. On the contrary, although the group of asymptomatic subjects with pheochromocytoma and the control group did not differ in the office BP, they differed significantly in the 24-hour systolic and diastolic BP ($P<0.05/<0.01$) and also in the relative systolic and diastolic night-time BP decline ($P<0.01/<0.01$). The differences in the values of 24-hour heart rate and its relative night-time decline were not significant between both pheochromocytoma groups or between patients with asymptomatic pheochromocytoma and the control group.

Our results showed that circadian BP variation is reduced in subjects with asymptomatic normotensive pheochromocytoma to the same degree as in case of subjects with a typical pheochromocytoma.

The mechanisms responsible for this phenomenon previously described only for hypertensive subjects with pheochromocytoma are not completely understood, although they allow some hypothesis to be considered (Spieker *et al.* 1993, Middeke and Schrader 1994). First, Bravo *et al.* (1990) hypothesized in their study that desensitization of the cardiovascular system to catecholamines might explain why some patients could be completely clinically asymptomatic. However, the absence of the circadian BP rhythmicity could mean that the desensitization is not complete. Second, Grassi *et al.* (1999) in their study on muscle sympathetic nerve activity postulated that the central depression of sympathetic outflow is induced by high circulating catecholamines. This might lead to the inability of an already inhibited sympathetic nerve activity to further decrease under the influence of centres that depress the adrenergic cardiovascular drive during sleep which could be responsible for the amelioration of the night-time BP decrease. Third, Munakata *et al.* (1999) suggested that altered sympathetic vascular regulation is central to the pathogenesis of orthostatic hypotension in pheochromocytoma, whereas cardiac vagal regulation acts to compensate it. In their study, performed in 12 subjects with pheochromocytoma, BP decreased significantly more upon standing in pheochromocytoma patients than in essential hypertensive or normotensive patients. This tendency to a more pronounced BP fall in the standing position in patients with pheochromocytoma could lead to a relative decrease of BP values during the active period of the day and, on the contrary, to higher night-time BP values which reflect higher sympathetic tone in pheochromocytoma than in normotensive subjects or in patients with essential hypertension. The circadian variation of heart rate remains unchanged because the baroreflex function in pheochromocytoma is not affected and the postural BP decline is accompanied by an increase of heart rate (Munakata *et al.* 1999).

In our study, the reduction of circadian BP rhythm was similar as in symptomatic pheochromocytoma patients. This might be due the partial desensitization of catecholamine receptors which could lead to a more pronounced postural BP falls during the day and to relatively lower day-time BP values than in normotensive patients or those with essential hypertension. Further investigation is needed to further clarify this observed phenomenon.

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