Twenty-Four Hour Blood Pressure Profile in Subjects with Different Subtypes of Primary Aldosteronism

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Summary

The aim of our study was to evaluate the potential differences in blood pressure (BP) profile in subjects with different forms of primary aldosteronism (PA). Simultaneously, we studied the effects of PA treatment on BP curve. We therefore monitored 24-hour ambulatory blood pressure values in 22 subjects with aldosterone-producing adenoma (APA), 22 subjects with idiopathic hyperaldosteronism (IHA) and 33 subjects with essential hypertension (EH) as controls. We found a significantly attenuated nighttime systolic BP decline in the APA group (P=0.02). Patients with IHA had lower nighttime systolic BP values (P=0.01) and also a diastolic BP decline (P=0.02) during the night in comparison with EH. We did not detect any significant differences in BP profile characteristics between APA and IHA. Specific treatment of primary aldosteronism (adrenalectomy, treatment with spironolactone) led to the normalization of the BP curve with a marked BP decline. Our study thus demonstrates a blunted diurnal BP variability in patients with primary aldosteronism the specific treatment of which normalized previously attenuated nocturnal BP fall.

Introduction

Nighttime bed rest is associated with blood pressure (BP) decline not only in normotensives but also in hypertensives, as it has been shown in previous studies performed by direct arterial pressure measurements or ambulatory blood pressure monitoring (ABPM) (Littler *et al.* 1975, Parati *et al.* 1987, Verdecchia *et al.* 1994, Staessen *et al.* 1997, Zanchetti 1997). Blunted BP fall during the night could be associated with a deteriorated health status in hypertensive subjects (Palatini *et al.* 1992, Verdecchia *et al.* 1994). The subjects with normal BP fall during the night are called "dippers" whereas those with attenuated BP nighttime decrease are referred as "non-dippers".

However, there is evidence about the absence or reduction of the nighttime BP decline in several pathophysiological conditions, e.g. autonomic failure, severe renal failure, pheochromocytoma, hyperthyreoidism, Cushing′s syndrome and diabetes mellitus type I and II (Mann *et al.* 1983, Imai *et al.* 1988, Munakata *et al.* 1988, Baumgart *et al.* 1989, Portaluppi *et al.* 1991, Fogari *et al.* 1993, Spieker *et al.* 1993, Middeke and Schrader 1994, Holl *et al.* 1999). In the case of the most common cause of endocrine hypertension – primary aldosteronism, conflicting reports have been published

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about the circadian BP profile (Tanaka et al 1983, Imai *et al.* 1992, Spieker *et al.* 1993, Veglio *et al.* 1993, Middeke and Schrader 1994, Penzo *et al.* 1994, Rabbia *et al.* 1997, Mansoor and White 1998, Uzu *et al.* 1998, Kimura *et al.* 2000). Most of the studies were focused on subjects with aldosterone-producing adenoma (APA) (Tanaka *et al.* 1983, Imai *et al.* 1992, Rabbia *et al.* 1997, Uzu *et al.* 1998, Kimura *et al.* 2000) but only few studies concerned both forms of primary aldosteronism (Spieker *et al.* 1993, Middeke and Schrader 1994, Mansoor and White 1998) or idiopathic hyperaldosteronism (IHA) (Veglio *et al.* 1993). But only one of these studies (performed on a smaller group of subjects) distinguished between APA and IHA (Rabbia *et al.* 1997).

The aldosterone secretion in both main forms of primary aldosteronism is regulated differently. APA is mostly ACTH-sensitive in contrast to IHA with its sensitivity to angiotensin II which results in different responses to various stimuli such as upright posture or captopril administration (Ganguly 1998, Stewart 1999). We have, therefore, tried to investigate the potential differences in the 24-hour BP profile between APA and IHA. A group of patients with essential hypertension (EH) served as controls. Furthermore, we have also assessed the effect of the specific treatment (surgical tumor removal or pharmacological treatment with spironolactone) on the circadian BP profiles in subjects with primary aldosteronism.

Methods

For the purpose of our study, we investigated 44 patients with primary aldosteronism, 22 patients with APA [including 2 subjects with unilateral adrenal hyperplasia because this condition is similar to APA (Otsuka *et al.* 1998)] and 22 patients with IHA. Our study was performed between 1994 and 1998. These patients were referred to our department because of suspected primary aldosteronism or to exclude secondary hypertension (spontaneous hypokalemia, drug-induced hypokalemia or refractory hypertension), and were investigated in the course of hospitalization. They underwent standard diagnostic procedures in our department which included repeated measurements of serum potassium and 24 h urinary potassium excretion as well as hormonal testing (aldosterone, cortisol and plasma renin activity) using commercially available RIA analysis. After the serum potassium values were corrected, the postural test [measurement of plasma renin activity, aldosterone and cortisol in the supine position and after 3 h of standing (Fontes *et al.* 1991)] and the captopril test [measurements of plasma renin activity and aldosterone before and 1 h after 25 mg captopril administration (Hambling *et al.* 1992)] were performed. Patients with an elevated plasma aldosterone/renin ratio (>50 ng/100ml//ng/ml/h) were considered as having primary aldosteronism and underwent computed tomography (CT) as well as, in certain cases, adrenal vein sampling. Twenty-two patients with confirmed tumors on CT scans were recommended for surgical treatment (open adrenalectomy). The final diagnosis of APA was later confirmed by histology (in two cases unilateral adrenal hyperplasia was found). One patient refused surgical treatment. The remaining subjects were diagnosed as having IHA with posturally induced aldosterone stimulation (more than 33 % above basal values) and bilateral microhyperplasia on the CT. As the control group, 33 patients with essential hypertension matched for age, body mass index, treatment status and office BP with the studied groups were chosen from our ABPM database. These patients had been referred to our department mainly because of severe hypertension and, in all cases, secondary hypertension was ruled out. The baseline characteristics of the studied groups of subjects with main forms of primary aldosteronism and the control group are shown in Table 1. The groups of subjects with primary aldosteronism did not differ from the control group of subjects with EH in age, treatment status, body mass index and office BP. The prevalence of organ complications (stroke) or accompanying disorders (diabetes mellitus type II, mild renal insufficiency, left ventricular hypertrophy) was also similar in all groups.

We tried to examine each patient (in the studied groups and the control group) without any antihypertensive medication that had been withdrawn at least two weeks before admission to our department. In certain cases, a monotherapy treatment with α-blockers was continued until the admission to our ward because of very high blood pressure levels.

After tumor removal, we repeated ABPM in 10 subjects with APA (one month after adrenalectomy on the average). Patients with IHA were treated with spironolactone (150 mg/day as the initial dose and 50 mg/day as long-term treatment) and repeated ABPM was performed approximately 6 months after starting the treatment with spironolactone.

Blood pressure measurements

Casual BP values were obtained in the sitting position by using a standard mercury sphygmo-

manometer. ABPM was performed with an oscillometric device SpaceLabs 90207 (SpaceLabs Medical, Richmond, USA) after correcting hypokalemia. BP was measured during the day (from 6:00 till 22:00 h) every 20 min and during the night (from 22:00 till 6:00 h) every 30 min. The patients were encouraged to go to bed at about 10 p.m. and to get up at 6 a.m. At the beginning and at the end of ABPM, BP values obtained with ABPM were checked against those obtained with a standard mercury sphygmomanometer; a maximum difference of ± 5 mm Hg was accepted as adequate agreement between the two methods.

We also tried to determine the non-dipping status in the same way as Mansoor and White (1998) did. We used following criteria:

1. the criterion of Verdecchia et al. (1994) (non-dipper = nighttime systolic and diastolic decline < 10 %),

2. the criterion of Staessen et al. (1997) (non-dipper = systolic and diastolic night-to-day ratio (in percentages) ≥ 100 %.

Statistical analysis

Data are shown means $\pm$ S.D. For comparisons of continuous variables among the studied groups and the control group we used two-sample t-test. We expressed the nighttime BP decline not only in absolute values but also in relative values, i.e. percentages. Categorical variables were compared between the groups by using the Fisher test. Changes in the paired values (data before and after the treatment) were analyzed using paired t-test and the McNamar test for categorical variables. P<0.05 values were considered significant.

Table 1. Baseline characteristics of patients with aldosterone-producing adenoma (APA), idiopathic hyperaldosteronism (IHA) and essential hypertension (EH).

	APA	IHA	EH
No. of subjects	22	22	33
Female/Male	12/10	2/20*** [#]	17/16
Age (years)	47±11	50±12	47±11
Body mass index (kg/m^2)	26±5	29±4	28±6
Treated with α-blockers	14	13	18
Systolic office BP (mm Hg)	164±25	169±17	161±23
Diastolic office BP (mm Hg)	109±13	110±12	105±15
Systolic 24-hour BP (mm Hg)	151±17	159±14**	147±16
Diastolic 24-hour BP (mm Hg)	99±10	101±18*	94±13

*Values are expressed as means $\pm$ S.D. IHA vs. EH: * P<0.05, ** P<0.01, *** P<0.001, APA vs. IHA: [#] P<0.001.*

Results

Values of 24-hour BP are shown in Table 1. Subjects with IHA had higher not only systolic but also diastolic BP than the control group [(systolic/diastolic BP) P=0.005/0.03]. As shown in Table 2, the nighttime systolic BP decline in the APA group was significantly lower than that of diastolic BP in comparison with the control group (absolute decline: P=0.02/0.13, relative decline: P=0.01/0.06). The incidence of dipping status in the APA group did not differ significantly from the control group in either criterion (A: nighttime BP decline >10 %; B: night-to-day ratio ≤ 100 %), but the difference according the criterion A was borderline (P=0.06). Subjects with IHA had a significantly lower

nighttime BP decline for systolic and diastolic BP compared to the control group (absolute decline: P=0.01/0.02, relative decline: P=0.007/0.01). The dipping status in the IHA group was exactly the same as in the APA group. The comparisons between the studied groups were not significant in any of the variables, although the 24-hour BP (systolic and diastolic) was higher in the IHA group.

The effects of surgical tumor removal in 10 subjects with APA on their blood pressure are shown in Table 3. Adrenalectomy led to a significant decrease of both office (P=0.005/0.002) and 24-hour BP (P=0.001/0.003). The nighttime BP decline was more pronounced after the surgery than before adrenalectomy. Similar results, which are shown in

Table 4 (office BP: P=0.003/0.02; 24-hour BP: P=0.013/0.008), were obtained in seven subjects with IHA who were treated with spironolactone.

Table 2. Nighttime blood pressure decline in patients with aldosteron-producing adenoma (APA), idiopathic hyperaldosteronism (IHA) and essential hypertension (EH).

	APA	IHA	EH
Absolute nighttime SBP decline (mm Hg)	6±11*	5±10*	13±11
Relative nighttime SBP decline (%)	3.3±7.7**	3.2±6.2**	9.2±8.6
Absolute nighttime DBP decline (mm Hg)	7±8	5±6*	11±10
Relative nighttime DBP decline (%)	6.6±7.8	5±5.9*	11.6±10.4
Dippers/non-dippers Criterion A	3/19	3/19	12/21
Dippers/non-dippers Criterion B	15/7	15/7	25/8

*SBP – systolic blood pressure, DBP – diastolic blood pressure. Dippers A are defined as > 10% decline of both SBP and DBP, Dippers B are defined as systolic and diastolic night-to-day ratio ≥ 100 %. Comparisons between APA and IHA are non-significant. Data are means ± SD. * $P<0.05$, ** $P<0.01$.*

Discussion

In the present study, we found a significantly lower nighttime decline of systolic BP in both forms of primary aldosteronism (APA and IHA) in comparison with the control group of subjects with essential hypertension. The nighttime decline of diastolic BP was significantly lower only in the IHA group compared to the control group. The difference in the nighttime decline of diastolic BP between the APA group and the control group was of a borderline significance. Considering diurnal BP variability by using the dipping status A and B, we only found borderline lower incidence according to the criterion A comparing the APA and IHA group separately to the control group. We found almost the same incidence of the dipping status according to both criteria A and B in the APA and IHA groups.

Our results differ from previous studies performed in the last few years on a smaller number of subjects (Imai *et al.* 1992, Spieker *et al.* 1993, Veglio *et al.* 1993, Penzo *et al.* 1994, Rabbia *et al.* 1997, Mansoor and White 1998, Kimura *et al.* 2000). In previous studies, any difference in diurnal variability between primary aldosteronism and essential hypertension was not found. A significant lower nighttime BP decline was mentioned only in three studies (Tanaka *et al.* 1983, Middeke and Schrader 1994, Uzu *et al.* 1998).

Table 3. Change of blood pressure and its nighttime decline in patients with aldosterone-producing adenoma (APA) before and after the tumor removal.

	APA before surgery	APA after surgery
Office BP (mm Hg)	163±26 / 107±12	137±13** / 91±13**
24-hour BP (mm Hg)	151±17 / 97±10	133±19** / 86±11**
Absolute nighttime BP decline (mm Hg)	4.3±12.1 / 5.2±7.3	7.7±9.1 / 6.5±8.1
Relative nighttime BP decline (%)	2.5±8.0 / 5.4±7.4	5.9±7.0 / 7.7±9.8
Dippers/non-dippers, Criterion A	1/9	3/7
Dippers/non-dippers, Criterion B	4/6	8/2

Blood pressure is expressed as systolic/diastolic. Data are means ± SD. ∗ P<0.05, ∗∗ P<0.01. For criteria A and B see Table 2.

Table 4. Change of blood pressure and its nighttime decline in subjects with idiopathic hyperaldosteronism (IHA) before and after the treatment with spironolactone.

	IHA before spironolactone	**IHA after spironolactone**
Office BP (mm Hg)	171±12 / 104±12	144±7∗∗ / 94±6∗
24-hour BP (mm Hg)	164±18 / 100±8	138±9∗ / 86±5∗∗
Absolute nighttime BP decline (mm Hg)	5.9±10.3 / 5.4±5.9	9.3±11.2 / 7.4±11.5
Relative nighttime BP decline (%)	4.0±6.2 / 5.5±5.6	6.5±8.0 / 7.8±12.0
Dippers/non-dippers Criterion A	1/6	2/5
Dippers/non-dippers Criterion B	5/2	5/2

Blood pressure is expressed as systolic/diastolic. Data are means ± SD. ∗∗ P<0.01. For criteria A and B see Table 2.

An explanation of our results may be provided by Uzu *et al.* (1998) who hypothesized that the attenuated nighttime BP decline with increased pressure natriuresis during the night could be a compensatory mechanism for diminished natriuresis during the daytime. When the same group of subjects with APA was on a low-salt diet or after adrenalectomy, a normal diurnal BP variability, such as in essential hypertension, was established. Similar results were obtained in subjects with APA on a controlled low-sodium diet (Kimura *et al.* 2000). This could be in agreement with the results of an earlier study, in which activation of the sympathetic nervous system in primary aldosteronism was excluded (Bravo *et al.* 1985).

Only Rabbia *et al.* (1997) distinguished APA and IHA in their study and their results were contrary to lour study. They found a significantly attenuated nighttime BP decline in the APA group, whereas in the IHA group the diurnal BP variability was similar as in essential hypertension. Results of our study performed on a greater number of subjects with APA were different from those of Rabbia and coworkers. The nighttime BP decline in the IHA group was diminished slightly more, and 24-hour BP values were higher than in the APA group. The similarity of the nighttime BP variability (assessed also as the dipping status) in both groups of subjects with primary aldosteronism could mean that only aldosterone could be responsible for the diminished nighttime BP decline regardless of the mechanism of aldosterone secretion. Interestingly, we did not found any significant differences in the severity of hypertension between APA and IHA, contrary to the traditional view concerning presumably higher aldosterone production and BP levels in APA (Kaplan 1998). The overall circadian BP profile was similar in APA and IHA. ABPM may thus not be of additional diagnostic value in the distinction between two major subtypes of APA.

Both adrenalectomy and spironolactone treatment significantly lowered office BP and 24-hour BP in both subtypes of primary aldosteronism and enhanced nighttime BP decline. We suppose that more studies with higher number of patients are needed to understand the problem thoroughly in relation to the change of diurnal BP variability after specific treatment of primary aldosteronism.

Furthermore, we found a significantly higher body mass index in subjects with IHA than in the APA group. This fact could explain slightly higher office and 24-hour BP in subjects with IHA.

Our study demonstrated a blunted diurnal BP variability in subjects with both main subtypes of primary aldosteronism. Specific treatment of primary aldosteronism led to a significant BP decrease and to the augmentation of attenuated nocturnal BP fall. The pathogenesis of the altered diurnal rhythm in primary aldosteronism remains to be determined.

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