Diurnal Blood Pressure Changes in Primary Aldosteronism – A Study of Ambulatory Blood Pressure Monitoring and Neurohormonal Changes

Pei-Ying Pai, Hsiang-Tai Chou, Shi-Sheng Tsou, Ching-Chu Chen[1], and Ting-Fu Wang

Division of Cardiology, and [1]Endocrinology, Department of Internal Medicine, China Medical College Hospital, Taichung, Taiwan, R.O.C.

The study was aimed to investigate the relationship between the 24-hour blood pressure and neurohormonal change in patients with secondary hypertension. Circadian blood pressure variation was studied in patients with chronic renal failure and primary aldosteronism. Ambulatory blood pressure was monitored every 10 minutes during daytime and every 30 minutes during nighttime. The daytime and nighttime systolic/diastolic blood pressures (SBP/DBP) in patients with primary hyperaldosteronism were significantly higher than those with primary hypertension (SBP:147±16 vs 125±11 mmHg, daytime; 142±23 vs 118±13 mmHg, nighttime; DBP: 96±18 vs 85±8 mmHg, daytime; 91±24 vs 81±9 mmHg, nighttime). In the renal form of secondary hypertension, the blood pressure did not reveal a significant difference with diurnal change in comparison with primary hypertension. The reduction in nocturnal blood pressure was less in primary hyperaldosteronism than in primary hypertension. Insufficient decrease of blood pressure during nighttime may warrant further investigation to diagnose secondary hypertension.

Key words

ambulatory BP monitor ,secondary hypertension ,neurohormonal

INTRODUCTION

In normal subjects and most essential hypertensives, circadian fluctuation of blood pressure (BP) has been well established [1,2]. The regulation of autonomic function over a 24-hour period is a result of feedback of circadian spontaneous rhythm. The neurohormonal system controls internal and external disturbances of the feedback mechanisms of regulative functions [3,4]. Evaluation of the circadian rhythm of blood pressure is particularly important in assessing the effects of treatment of hypertension and in studying the mechanisms of hypertension. Ambulatory blood pressure monitoring has been proved useful in terms of characterization of blood pressure profiles in normotensive and hypertensive subjects, evaluation of patients with mild or labile hypertension, degree of blood pressure elevation, prognosis of hypertension, and assessment of hypertension management. The prognostic implications of

Received: November 14, 1997 Revised: December 30, 1997
Accepted: January 15, 1998
Address reprint requests to: Pei-Ying Pai, Division of Cardiology, Department of Internal Medicine, China Medical College Hospital, No 2,Yuh-Der Road, Taichung, Taiwan R.O.C.

abnormal diurnal variations in blood pressure are not fully established. An absence of nocturnal reductions in blood pressure has been noted in patients under several disease states, such as those with malignant hypertension [5], diabetes mellitus [6], pheochromocytoma [7], preeclampsia [8], heart transplants [9] and cerebral stroke [10]. In the present study, we applied ambulatory BP monitor to subjects with normal blood pressure, essential hypertension, primary aldosteronism (PA), and chronic renal failure (CRF) to examine the relationship between the 24-hour blood pressure rhythm and neurohormonal change in patients with secondary hypertension.

MATERIALS AND METHODS

Subjects

From April 1992 to March 1997, we monitored for 24-hour the blood pressure on subjects (n=72) grouped accordingly: normotensives (n=22), patients with untreated mild-to-moderate essential hypertension (casual BP values between 140/90 and 180/110 mmHg, n=36), patients with chronic renal failure without dialysis treatment (n=8), and patients with primary aldosteronism (n=6). The known duration of increased blood pressure in untreated essential hypertension ranged from six months to three years. In the last two groups, diagnosis was made by clinical features and results of hormonal, radiological, and general biochemical tests. For screening of primary aldosteronism and renal vascular hypertension, plasma renin activity and plasma aldosterone concentration were measured and a stimulation test with captopril (50mg) was performed. On patients with primary aldosteronism, computed tomography scan and adrenal vein sampling were performed.

24-Hour blood pressure monitoring

We monitored 24-hour BP using a portable noninvasive recorder (Oxford Medilog ambulatory blood pressure monitoring system) in each study group. BP and heart rates recording were obtained as described by Pai et al. [11]. Briefly, BP was measured every 10 minutes during the daytime (from 06:01 to 21:59) and every 30 minutes during the night time (from 22:00 to 6:00). All subjects were allowed their usual activities in the ward. All antihypertensive medications were withdrawn at least 72 hours before ambulatory BP study from patients with primary aldosteronism and chronic renal failure.

Diurnal change in neurohormonal change

We measured morning and evening cortisol level, plasma aldosterone, and plasma renin activity at 8:00 and 17:00-18:00, respectively. The diurnal variation of these neurohormonal secretions was correlated with ambulatory blood pressure level.

Echocardiography study

Echocardiography and Doppler recordings were made with a Toshiba SSA-270A 2.5MHz sector scanner. M-mode echocardiograms were recorded on a strip chart recorder at 50 mm/sec. All measurements including systolic and diastolic function were obtained as described by Pai et al. [11]. Systolic function was determined by measuring percent fractional shorting of the left ventricular internal dimension (FS) and observing regional wall motion from 2-D echocardiograms. No subjects in this series had segmental wall motion abnormality.

Statistics

All values were expressed as the mean $\pm$ standard deviation (SD). Averages of ambulatory SBP, DBP and heart rate variables during daytime (06:01-21:59) and nighttime (22:00-06:00) were compared between groups by unpaired Student t test. Amplitudes of nocturnal fall of SBP or DBP (average BP during daytime - average BP during nighttime) were also compared between groups. Linear regression analysis was used to determine the significance of correlation between

Table 1 The clinical characteristics of subjects in each study group

	Age (years)	Sex M/F	Cr (mg/dl)	LVEDd (mm)	MMT (mm)
NT	44±11	12/10	0.7±0.2	45±4	9±1
EH	51±13	21/15	0.9±0.3	48±5	10±2
PA	40±8	3/3	0.8±0.2	48±6	12±2
CRF	46±16	1/7	8.1±4.2	54±5*	11±2

Abbreviations, NT: normotension, EH: essential hypertension, PA: primary aldosteronism, CRF: chronic renal failure, Cr: serum creatinine, LVEDd: left ventricular end-diastolic dimension, MMT: mean myocardial thickness,
* $p < 0.05$. compared with normotensive.

Table 2 Clinical characteristics of patients with primary aldosteronism

	Sex	Age	Site of adenoma	PAC1 (pg/ml)	PAC2 (pg/ml)	PRA1 (ng/ml/hr)	PRA2 (ng/ml/hr)	Cortisol1 (mg/dl)	Cortisol2 (mg/dl)	K (meq/L)
1	M	35	R	404	189	4.15	1.04	14.9	9.2	3.3
2	F	46	L	300	126	1.22	2.59	12.6	5.7	3.0
3	M	36	L	284	192	2.32	0.29	14	5	2.8
4	F	40	L	426	126	3.60	1.87	16.4	6	3.0
5	M	30	R	548	97	3.56	3.0	9.8	5.7	3.3
6	F	33	L	211	95	4.45	3.7	13.5	12.4	3.4

Abbreviations, R: right, L: left, PAC1: plasma aldosterone concentration at 8:00, PAC2: plasma aldosterone concentration at 18:00, PRA1: plasma renin activity at 8:00, PRA2: plasma renin activity at 18:00, Cortisol1: serum cortisol level at 8:00, Cortisol2: serum cortisol level at 18:00, K: plasma potassium concentration.

independent variables. Results with p value less than 0.05 were considered statistically significant.

RESULTS

Clinical Characteristics and Circadian Variation of BP and HR in Normal Subjects and Patients with Essential Hypertension

The clinical characteristics of the subjects in each study group are shown in **Table 1**. A clear nocturnal fall in SBP, DBP and HR was observed in normal subjects and untreated essential hypertensive patients.

Circadian Variation of BP and HR in Patients with Primary Aldosteronism

The characteristics of patients with primary aldosteronism are shown in **Table 1** and **Table 2**. As shown in **Fig. 1**, nocturnal fall of blood pressure and heart rate was observed in patients with PA, but the amplitude of the nocturnal fall of blood pressure of patients with PA was significantly less than of patients with essential hypertension (**Table 3**).

Table 3 Ambulatory blood pressure values and the amplitude of nocturnal fall in blood pressure or heart rate in each study group

	SBP(mmHg)			DBP(mmHg)			HR(bpm)		
	Daytime	Nighttime	△SBP	Daytime	Nighttime	△DBP	Daytime	Nighttime	△HR
NT	105±8	96±11	10±9	69±6	63±7	6±5	77±8	63±7	15±7
NT	125±11	118±13	8±12	85±8	81±9	5±8	76±10	68±9	9±8
PA	147±16*	142±23*	5±14†	96±18*	91±24*	5±8	84±12	73±14	11±2
CRF	135±12*	127±19*	9±10	89±10	84±11	6±10	85±6	79±7	6±8

Abbreviations, NT: normotension, EH: essential hypertension, PA: primary aldosteronism, CRF: chronic renal failure, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, △SBP: nocturnal fall in SBP, △DBP: nocturnal fall in DBP, △HR: nocturnal fall in HR

* $p < 0.01$, † $p < 0.05$, compared with essential hypertension.

Circadian Variation of BP and HR in Patients with Chronic Renal Failure

The characteristics of patients with chronic renal failure are shown in **Table 1**. As shown in **Fig. 1**, nocturnal fall of blood pressure and heart rate was observed in patients with CRF. The daytime SBP and DBP were significantly higher, but the amplitude of the nocturnal fall of blood pressure of patients with CRF were not significantly different compared with patients with essential hypertension (**Table 3**).

Correlation Among Ambulatory Blood Pressure and the Diurnal Change of Neurohormonal Secretion in Patients with Primary Aldosteronism

The ambulatory blood pressure and heart rate did not show any correlation with the diurnal variation of plasma aldosterone level (r=0.10 for daytime SBP, r=0.27 for nighttime SBP; r=0.19 for daytime DBP, r=-0.20 for nighttime DBP). The ambulatory blood pressure even showed a non-significant inverse correlation with plasma renin activity and cortisol level both in daytime and nighttime (r=-0.32 for daytime SBP, r=-0.32 for nighttime SBP with plasma renin activity; r=-0.27 for daytime SBP, r=-0.24 for nighttime SBP, r=-0.33 for nighttime DBP with cortisol).

DISCUSSION

When nocturnal pressure does not fall, both the myocardium [12] and the cerebral circulation [13] may be harmed. Whatever the mechanism, patients with secondary hypertension may not experience a nocturnal fall in blood pressure [1,14]. Although the controlling mechanism of circadian BP rhythm remains uncertain, it would seem likely that several factors are involved. These may include neurohormonal changes acting through the sympathetic nerve system, the adrenocorticotropic hormone (ACTH)-cortisol system [15], the vasopressin system, and the cardiovascular depressor mechanism.

The circadian BP variation in renovascular hypertension and primary aldosteronism patients was similar to that in normal subjects and essential hypertensive patients [16]. Many studies have also confirmed that plasma renin activity and plasma aldosterone concentration were the highest in the morning hours and low in the evening in normal subjects and patients with primary aldosteronism [17-20]. Our results showed similar circadian variation of plasma aldosterone concentration and renin activity in patients with primary aldosteronism. We therefore assumed that the circadian rhythm of BP in primary aldosteronism is similar to that in normal subjects and essential hypertensive patients. Results from other studies were, however, quite different from

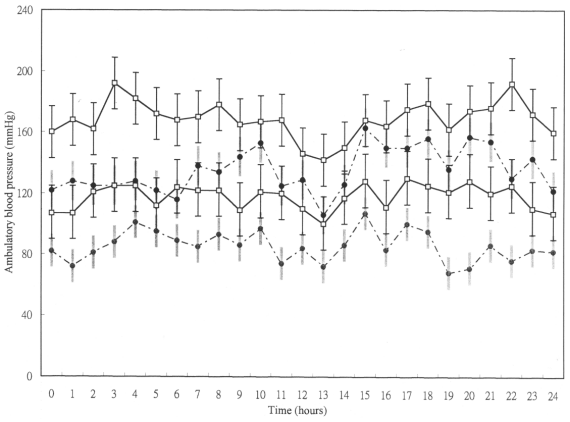

Fig. 1 Ambulatory blood pressure in patients with primary aldosteronism(PA) and chronic renal failure(CRF). —□— SBP of PA, —□— DBP of PA, —●— SBP of CRF, —●— DBP of CRF,

ours. According to Tanaka report [21], both SBP and DBP of 11 patients with primary aldosteronism rose in the evening. In our study, the SBP and DBP were lower than those found in Tanaka study (SBP: 172-175 mmHg, DBP: 101-103 mmHg), but higher than those in Imai et al [16] (SBP: 135±19 mmHg, DBP: 85±14 mmHg) and Nicholls ' [22] (DBP: 87±16 mmHg) studies. We demonstrated a blunted circadian rhythm of systolic blood pressure in primary aldosteronism and also found weak inverse correlation between ambulatory blood pressure variation and circadian change of neurohormonal secretion, which may suggest that the renin-angiotensin system does not mediate the circadian blood pressure variation in primary aldosteronism. Imai (16) has proposed that the difference between studies may be due to the difference in blood pressure level and consequently due to the difference in severity of hypertension, which might explain the differences between essential hypertension and primary aldosteronism in the present study. Inadequate withdrawal of sympathetic tone during sleep may play a major role in the mechanism responsible for the decreased nocturnal fall in blood pressure.

Renal and renovascular diseases appear to raise blood pressure by a complex interaction between sodium and volume status and the production of renin and angiotensin II [23]. In patients with end-stage renal disease or with chronic renal failure treated by hemodialysis, the circadian blood pressure rhythm is altered [24]. In our group, the circadian rhythm of chronic renal failure without hemodialysis treatment had higher blood pressure but well-preserved circadian rhythm in comparison with essential hypertensive group. We also found a larger left ventricular end-diastolic dimension (LVEDd) with echocardiography, which indicates volume overload status. We, therefore, suggest that volume status rather than disturbance in renal excretory function has much impact on the circadian blood pressure rhythm on patients with chronic renal failure.

There are potential limitations in the present study. First, there may be a selection bias resulting from preexisting blood pressure level in different groups. Because other forms of secondary hypertension (e.g. renovascular hypertension, and hyperthyroidism) were not under study, we cannot exclude the impact of neurohormonal change to diurnal rhythm of blood pressure at all. Second, because the relevant hormonal values in patients with chronic renal failure were not measured, it was not clear whether a disturbance in hormonal changes can be related to the circadian blood pressure in this group. Third, the antihypertensive treatment was held only 72 hours before applying ambulatory blood pressure monitoring, and the long acting drugs, especially excreted via kidney, may not be eliminated completely during study and may have interfered the circadian rhythm on patients with chronic renal failure. Further investigation of patients before and after hemodialysis and evaluation of BP reduction with antihypertensive drugs might help to understand the mechanism of hypertension in uremic patients.

Considering the findings of the present study, hypertensive patients without adequate nocturnal fall of blood pressure will have higher blood pressure at night than those who retain normal circadian rhythm. Distinguish one from another by the pattern of the blood pressure rhythm will, however, be difficult. Further analysis of phase shift or change in the amplitude of the circadian blood pressure using ambulatory blood pressure monitoring might be of value in identifying patients with altered circadian rhythm and statistical significance determined.

It might be concluded that the renin-angiotensin-aldosterone system neither primarily nor secondarily mediated the circadian BP variation in patients with primary aldosteronism. In secondary hypertension, blood pressure monitoring during daytime and nighttime is particularly useful for evaluating frequently severe nocturnal hypertension, that may warrant further investigation and treatment.

REFERENCES

1. Baumgart P, Walger P, Dorst KG, et al: Can secondary hypertension be identified by twenty-four hour ambulatory blood pressure monitoring ? ***J Hypertens*** 1989;7(suppl 3):S25-8.
2. Pickering TG: The clinical significance of diurnal blood pressure variations: dippers and non-dippers.***Circulation*** 1990;81:700-2.
3. Parmeggani PL: Physiological risks during sleep. In: Peter JH, Penzel P, Podszus P, eds. Sleep and health risk. Berlin: Springger-Verlag, 1991:119-23.
4. Littler WA, Honour AJ, Carter RD, et al: Sleep and blood pressure. ***Br Med J*** 1975;3:346-8.
5. Goss P, Jullien E, Reyaud P, et al: Circadian rhythm of blood pressure: importance of the severity and not the cause of arterial hypertension. ***Arch Mal Coeur*** 1988 ; 81:247-50.
6. White WB: Diurnal blood pressure and blood pressure variability in diabetic normotensive and hypertensive subjects ***J Hypertens*** 1992;10(supp1):S35-41.
7. Littler WA, Honour AJ: Direct arterial pressure, heart rate, and electrocardiogram in unrestricted patients before and after removal of a pheochromocytoma. ***Q J Med*** 1974;43:441-9.
8. Redman CWG, Beilin LJ, Bonnar J: Reversed diurnal blood pressure rhythm in hypertensive pregnancies. ***Clin Sci Mol Med*** 1976;51:S687-9.
9. Reeves RA, Shapiro AP, Thompson ME, et al: Loss of nocturnal decline in the blood pressure after cardiac transplantation. ***Circulation*** 1986;73:401-8.
10. LJ, Tseng YZ,Chiang FT, et al: Altered circadian rhythm of blood pressure in patients with cerebral stroke. ***Am J Noninvas Cardiol*** 1992;6:62-5.
11. Pai PY, Chou HT, Tsou SS, et al: The prognostic value of ambulatory blood pressure monitoring in untreated mild-to-moderate hypertensive patients: correlation with echocardiography. ***Chin Med J(Taipei)*** 1994;54:93-9.
12. Verdecchia P, Schillaci G, Guerreri M, et al: Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. ***Circulation*** 1990;81:528-36.
13. Shimada K, Kawamoto A, Matsubayashi K, et al: Silent cerebrovascular disease in the elderly: correlation with ambulatory pressure. ***Hypertension*** 1990;16:692-9.
14. Imai Y, Abe K, Munakata M, et al: Does ambulatory blood pressure monitoring improve the diagnosis of secondary hypertension? ***J Hypertens*** 1990;8(suppl 6): S71-5.
15. Imai Y, Abe K, Sasaki S et al: Altered circadian blood pressure in patients with cushing ' s syndrome ***Hypertension*** 1988;12:11-9.
16. Y Imai, K Abe, S Sasaki, et al: Circadian blood pressure variation in patients with renovascular hypertension or primary aldosteronism. ***Clin Exper Hyper-Theory and Practice*** 1992;A14:1141-67.
17. Michelakis AM, Horton R: The relationship between plasma renin and aldosterone in normal man. ***Circ Res*** 1970;36 & 37 (suppl I): I185-94.
18. Katz FH, Romfh P, Smith JA: Diurnal variation of plasma aldosterone, cortisol and renin activity in supine man. ***J Clin Endocrinol Metab*** 1975;40:125-34.
19. Cain JP, Tuck ML, Williams GH, et al: The regulation of aldosterone secretion in primary aldosteronism. ***Am J Med*** 1972;53:627-37.
20. Modlinger RS, Sharif-Zadeh K, Schneider G, et al: Circadian rhythm of plasma renin activity in primary aldosteronism. ***J Clin Endocrinol Metab*** 1976;42:361-4.
21. Tanaka T, Natsume T, Shibata H, et al: Circadian rhythm of blood pressure in primary aldosteronism and renovascular hypertension -----analysis by the Cosinor method ***Jan Cir J*** 1983;47:788-94.
22. Nicholls MG, Espiner EA, Ikram H, et al: Hormone and blood pressure relationships in primary aldosteronism. ***Clin Exp Hypertens*** 1984;A6:1441-58.
23. Davies DL, Schalekamp MA, Beevers DG, et al: Abnormal relation between exchangeable sodium and the renin-angiotensin system in malignant hypertension and in hypertension with chronic renal failure. ***Lancet*** 1973;1:683-8.
24. Imai Y, Munakata M, Abe K, et al: The circadian blood pressure variation in patients with disturbance of renin-angiotensin-aldosterone system and with renal disease. (in Japanese) ***Annual Review of Nephrology*** 1990, 141- 51.

原發性醛類酯醇過多症日夜血壓變化：運用攜帶式二十四小時血壓監視研究與神經荷爾蒙之關係

白培英　周湘台　鄒吉生　陳清助[1]　王廷輔

中國醫藥學院附設醫院　內科部　心臟內科　[1]新陳代謝科

為了解次發性高血壓患者之血壓變化與標的器官傷害之關係並評估其神經荷爾蒙之變化，經由非侵襲性之血壓監視器測得異常之血壓變化，作為臨床上篩檢次發性高血壓之診斷工具，並經由神經荷爾蒙之變化，了解次發性高血壓異常之血壓變化機轉，期能尋求更有效治療方式。本研究即利用非侵襲性之24小時血壓監視器,記錄在一般活動下之次發性高血壓患者24小時之血壓變化，並檢驗其血中不同時段神經荷爾蒙之濃度對血壓值變化及對標的器官傷害的影響。本計畫取樣自門診異常高血壓患者經檢查有次發性之原因包括原發性醛類酯醇過多症或慢性腎衰竭之病人安排接受24小時血壓監視，心臟超音波檢查及神經荷爾蒙之檢驗。在原發性醛類酯醇過多症之病人，白天及夜晚之血壓都比原發性高血壓患者高(白天SBP:147±16 vs 125±11mmHg, DBP: 96 ±18 vs 85±8mmHg; 夜晚SBP:142±23 vs 118±13mmHg, DBP 91±24 vs 81±9mmHg, $p<0.05$)，在慢性腎衰竭之病人與原發性高血壓患者比較，他們的日間血壓有較顯著之差異。在原發性醛類酯醇過多症之病人，夜晚之收縮壓下降之幅度並不顯著，不見有日夜之變化。因此，對於夜間血壓下降不顯著之病人應該更仔細去追查及治療潛在之次發性病因。

關鍵字

24小時血壓監視，次發性高血壓，神經荷爾蒙

聯絡作者：白培英

地　　址：台中市育德德路2號

中國醫藥學院附設醫院 內科部 心臟內科

收文日期：11/14/1997　　修改日期：12/30/1997

接受日期：1/15/1998