Altered circadian blood pressure rhythm in patients with Cushing's syndrome

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Altered Circadian Blood Pressure Rhythm in Patients with Cushing's Syndrome

YUTAKA IMAI, KEISHI ABE, SHUICHI SASAKI, NAOYOSHI MINAMI, MINORU NIHEI, MASANORI MUNAKATA, OSAMU MURAKAMI, KATSUHIKO MATSUE, HIROSHI SEKINO, YUKIO MIURA, AND KAORU YOSHINAGA

SUMMARY The circadian blood pressure rhythm was compared in patients with Cushing's syndrome, essential hypertension, and primary aldosteronism. In patients with essential hypertension or primary aldosteronism, a clear nocturnal fall in systolic and diastolic blood pressure and heart rate was observed. This fall was seen in untreated subjects as well as in patients receiving combined treatment with a calcium antagonist, diuretic, converting enzyme inhibitor, α-blocker and β-blocker, or sympatholytic drug. In these groups, there was a positive correlation between heart rate and systolic or diastolic blood pressure. On the other hand, in patients with Cushing's syndrome, there was no nocturnal fall in blood pressure but in some patients a rise was observed. In all patients there was a nocturnal fall in heart rate. Thus, there was no significant correlation between heart rate and blood pressure in these patients. Exogenous glucocorticoid eliminated the normal nocturnal fall of blood pressure in patients with chronic glomerulonephritis or systemic lupus erythematosus. These results suggest that the changed circadian blood pressure pattern in patients with Cushing's syndrome is not due to antihypertensive treatment or to the mineralocorticoid excess accompanying this disease, but it is attributable to excess glucocorticoid or the associated disturbance in the adrenocorticotropic hormone-glucocorticoid system (or both). This conclusion also implies that the normal circadian rhythm of blood pressure may be regulated at least in part by the adrenocorticotropic hormone-glucocorticoid system. (Hypertension 12: 11-19, 1988)

KEY WORDS • Cushing's syndrome • blood pressure • heart rate • circadian rhythm • blood pressure monitoring • essential hypertension • primary aldosteronism • cortisol

Circadian fluctuations of blood pressure (BP) have been postulated, and it has been shown that BP reaches a nadir at approximately 0300, begins to rise again at 0500, and reaches its highest level at about 0900. The latter increase is said not to be associated with physical activity. Several researchers have claimed that the fluctuations observed in BP are related to daily activities such as sleep and physical exertion rather than the presence of an independent BP rhythm related to time alone. An absence of any sleep-related reductions in BP has been noted in several disease states, such as malignant hypertension, pheochromocytoma, preeclampsia, and autonomic failure, and this fact is frequently cited against the hypothesis of a circadian BP rhythm that is affected by physical activities and the length and depth of sleep. Whatever the explanation, the most conspicuous and consistent finding in all studies on normal subjects and essential hypertensive patients is a nocturnal fall in BP when subjects are asleep. In the present study, we tentatively refer to it as the circadian BP rhythm. Although the controlling mechanisms of circadian BP rhythm remain uncertain, it would seem likely that several factors are contributing. These may include neurohumoral changes acting through the sympathetic nervous system, the adrenocorticotropic hormone (ACTH)–cortisol system, the renin-angiotensin-aldosterone system, the vasopressin system, and cardiovascular depressor mechanisms. In the present study, we examined the...
relationships between the circadian BP rhythm and the disturbance of the pituitary-adrenal axis. BP was monitored for 24 hours in patients with Cushing's syndrome, as a model of the disturbed ACTH-cortisol system. We also investigated the influence of excess glucocorticoid on circadian BP rhythm. The 24-hour BP was measured with a noninvasive automatic monitoring device, which we have developed recently based on the volume oscillometric technique, recording the BP indirectly at the finger.\(^1\)

### Subjects and Methods

In the present study, we monitored 24-hour BP in patients with Cushing's syndrome, primary aldosteronism, or essential hypertension. The ages and preexisting treatments in these subjects are summarized in Table 1. In the first two groups, diagnosis was made by clinical features and results of hormonal, radiological, and general biochemical tests. The characteristics of patients with Cushing's syndrome and those with primary aldosteronism are shown respectively in Tables 2 and 3. For diagnosis of Cushing's syndrome, the 8-mg dexamethasone suppression test as well as the single bedtime 1-mg dexamethasone suppression test was performed. As shown in Table 2, plasma cortisol was not suppressed below 1 \(\mu\)g/dl by dexamethasone in all patients with Cushing's syndrome. To differentiate the type of Cushing's syndrome, plasma ACTH was measured. For screening of primary aldosteronism, plasma renin activity and plasma aldosterone concentration were measured and stimulation tests for renin release with furosemide were performed.

### Table 2. Clinical Data in Patients with Cushing's Syndrome

<table>
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<tr>
<th>Patient no., sex, age (yr)</th>
<th>Diagnosis</th>
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<tr>
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<td>Ectopic</td>
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</table>

Dexa = dexamethasone; PRA = plasma renin activity; Ang I = angiotensin I; PAC = plasma aldosterone concentration; NE = norepinephrine; E = epinephrine; 17-OHCS = 17-hydroxycorticosterone; R = right; L = left; Pit A = pituitary adenoma; AA = adrenal adenoma; ectopic = ectopic ACTH-producing tumor; ND = not detectable.
As shown in Results, the BP level of a calcium antagonist in combination with a- or sympatholytic drug on the circadian BP rhythm were examined in patients with essential hypertension. Therefore, the quality and quantity of antihypertensive drug regimen. Thus, the effects of aldosterone antagonists on BP in patients with Cushing’s syndrome treated with antihypertensive drugs (Group 2). As shown in Results, the BP level in patients with Cushing’s syndrome seems higher when compared with that of essential hypertensive patients, whether treated with combined antihypertensive drugs or not. Therefore, we gathered essential hypertensive patients who had undergone at least calcium antagonist treatment and whose averaged daytime systolic blood pressure (SBP) was more than 155 mm Hg (Group 3) and compared their circadian BP rhythm with that of the patients with Cushing’s syndrome. The quality and quantity of antihypertensive drugs were expressed collectively as a drug score. The dose of a drug that effectively treats mild hypertension was arbitrarily assigned a value of 1 point. This point system has been reported elsewhere.11

In the present study, the quality and quantity of sleep were also critical points in evaluating the nocturnal change in BP. Patients who complained of sleep disturbance on the day of BP monitoring were not included in the study. In two patients with Cushing’s syndrome, overnight monitoring of electroencephalogram (EEG) as well as 24-hour BP monitoring was performed. In five patients with Cushing’s syndrome, 24-hour BP monitoring was performed twice, with and without nitrazepam treatment (10 mg at 2300). In six patients with chronic glomerulonephritis or systemic lupus erythematosus, the effect of prednisolone (45.0 ± 1.7 [mean ± SD] mg, once in the morning every day [0800] over a week or more; 54.2 ± 22.0 days [mean ± SD]) on circadian BP rhythm was examined. The dose of prednisolone at which BP monitoring was done was shown. The dose was not necessarily maintained at the same level during the period of prednisolone treatment.

All BP monitorings were performed in a ward setting. Nearly all the subjects were allowed their usual activities in the ward. However, one patient with ectopic ACTH-producing tumor was confined to bed throughout the day. Another with adrenal Cushing’s syndrome (Patient 14) was asked to keep recumbent as much as possible during the BP monitoring sessions throughout the day. Another with adrenal Cushing’s syndrome was confined to bed during the BP monitoring setting. Nearly all the subjects were allowed their usual activities in the ward.

In all, 29 monitoring sessions were performed in 16 patients with Cushing’s syndrome. Since several patients with Cushing’s syndrome had a diastolic BP (DBP) above 120 mm Hg, a study in the absence of antihypertensive medication was not possible. In six of the 29 monitoring sessions, patients were not treated with antihypertensive drugs. In the remaining monitoring sessions several kinds of antihypertensive drugs were used. The circadian BP rhythm in patients with several types of Cushing’s syndrome (Groups 4, 5, and 6), including those treated with antihypertensive drugs and without benzodiazepine, was compared with that in subjects with untreated Cushing’s syndrome, untreated essential hypertension (Group 1), or essential hypertension treated with antihypertensive drugs (Group 2). In most patients with Cushing’s syndrome some kind of calcium-antagonistic vasodilator was used as a part of the antihypertensive drug regimen. Therefore, the effects of a calcium antagonist in combination with a diuretic, converting enzyme inhibitor, -blocker and -blocker, or sympatholytic drug on the circadian BP rhythm were examined in patients with essential hypertension (Group 2). As shown in Results, the BP level in patients with Cushing’s syndrome seems higher when compared with that of essential hypertensive patients, whether treated with combined antihypertensive drugs or not. Therefore, we gathered essential hypertensive patients who had undergone at least calcium antagonist treatment and whose averaged daytime systolic blood pressure (SBP) was more than 155 mm Hg (Group 3) and compared their circadian BP rhythm with that of the patients with Cushing’s syndrome. The quality and quantity of antihypertensive drugs were expressed collectively as a drug score. The dose of a drug that effectively treats mild hypertension was arbitrarily assigned a value of 1 point. This point system has been reported elsewhere.11

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### Table 3. Clinical Data in Patients with Primary Aldosteronism

<table>
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<tr>
<th>Patient no., sex, age (yr)</th>
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<th>Plasma Na (mEq/L)</th>
<th>Plasma K (mEq/L)</th>
<th>PRA (ng Ang I/ml/dl)</th>
<th>PAC (ng/dl)</th>
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PRA = plasma renin activity; Ang I = angiotensin I; PAC = plasma aldosterone concentration; LAA = left adrenal adenoma; RAA = right adrenal adenoma.
monitoring session when an overnight EEG was performed.

BP Monitoring

The device used in the present study (BP-100 system, ME Commercial, Tokyo, Japan) can automatically monitor SBP and mean BP in the human finger using the volume-oscillometric method. Calculated DBP is also available. The theoretical basis of this method and technical details of this instrument have been described elsewhere.\(^1\)\(^2\) Briefly, the method is designed to measure BP by detecting the local arterial volume pulsation using a photoelectric plethysmograph that is placed just below the occluding cuff. During a gradual increase or decrease in the cuff pressure, the photoplethysmographic pulsations characteristically change in amplitude and the systolic end point and the point showing the maximum amplitude can be clearly determined. The cuff pressure values corresponding to the systolic end point and the maximum amplitude are in good agreement with SBP and mean BP in the arterial segment concerned.\(^1\)\(^2\)\(^3\) Performance of this device and its stability for long-term BP monitoring have been reported elsewhere.\(^4\)

In the present study, BP was monitored every 5 minutes for 24 hours. Patients had breakfast at about 0730, lunch at about 1130, and an evening meal at 1700. All lights were put out at 2100, and patients were awakened at 0600 by morning calls.

Biochemical Methods

Duplicate measurement of plasma ACTH (CEA-IRE-Sorin, Gif-sur-Yvette, France), cortisol (Eiken, Tokyo, Japan), and aldosterone concentrations (Dynabot, Tokyo, Japan) were made using commercial radioimmunoassay kits. Plasma renin activity was determined with a modification of Haber's method.\(^4\) Urinary catecholamines were measured by a sensitive fluorometric method.\(^5\)

Analytical Methods

Time-trend charts were constructed for SBP, DBP, and heart rate (HR) averaged every hour by computer for each disease group. Averages of SBP, DBP, and HR during waking hours (0600–2059) were compared with nighttime values (2100–0559) using one-way analysis of variance and Student's \(t\) test. A linear regression analysis was done on the BP and HR data.

Results

Circadian Rhythm of BP and HR in Patients with Essential Hypertension (Group 1)

Figure 1A is a typical time-trend chart of BP and HR in a subject with untreated essential hypertension. As shown in Figure 2A, a clear nocturnal fall in SBP, DBP, and HR and two daytime peaks, one in the morning (0600–0859) and the other in the late afternoon (1600–1859), were observed in untreated patients with essential hypertension. The changes in BP were well correlated with those in HR (SBP: \(r = 0.97, p < 0.01\); DBP: \(r = 0.94, p < 0.01\)). BP and HR gradually fell during the evening, reached a nadir between 0100 and 0159, and then began to rise again gradually.

Essential hypertensive patients who were treated with combined antihypertensive drugs (Group 2; Figure 2B) or whose averaged daytime SBP was more than 155 mm Hg (Group 3; Figure 2C) demonstrated almost similar circadian rhythm of BP and HR to that in untreated subjects with essential hypertension (Group 1; Figure 2A). In the former two groups the changes in BP were correlated with
FIGURE 2. Circadian rhythm of SBP, DBP, and HR in 38 untreated subjects with essential hypertension (A), in 32 essential hypertensive patients treated with combined antihypertensive drugs (B), and in 12 essential hypertensive patients whose averaged daytime SBP was more than 155 mm Hg (C).

Circadian Rhythm of BP and HR in Patients with Cushing’s Syndrome

Figure 3A demonstrates the circadian rhythm of BP and HR in six untreated subjects with Cushing’s syndrome (Patients 6, 9–13). The circadian rhythm of BP and HR in patients with pituitary Cushing’s syndrome (Group 4; 14 measurements in 11 patients) and adrenal Cushing’s syndrome (Group 5; 4 measurements in 4 patients) is also demonstrated in Figures 3B and C, respectively. In the patients with pituitary Cushing’s syndrome, multiple measurements in a single patient were averaged, and then these average values were used for the group analysis. Figure 1B is an actual time-trend chart for BP and HR in a patient with an ectopic ACTH-producing tumor (Patient 16). As shown in these figures, BP gradually rose between midnight and early morning, reaching a peak just before or after awakening of the patients with Cushing’s syndrome of different pathogenesis. Although the patterns of circadian BP rhythm in Cushing’s syndrome were very different from those in subjects with treated or untreated essential hypertension, the circadian HR rhythm in the former was essentially the same as that in the latter.

Although in many patients with Cushing’s syndrome 24-hour BP monitoring was performed under antihypertensive treatment (see Table 1), the present results demonstrated that the treatment did not affect the circadian BP rhythm in patients with Cushing’s syndrome (Figure 3A vs Figures 3B and 3C). A linear regression analysis demonstrated that there was no correlation between BP and HR in subjects with untreated Cushing’s syndrome (SBP: $r = 0.04$, $p < 0.01$; DBP: $r = 0.08$, $p < 0.01$; Group 3: SBP, $r = 0.94$, $p < 0.01$; DBP, $r = 0.88$, $p < 0.01$).

Effect of Exogenous Glucocorticoid on the Circadian Rhythm of BP and HR in Patients with Chronic Glomerulonephritis or Systemic Lupus Erythematosus

As shown in Figure 4B, the pattern of circadian BP rhythm in patients with chronic glomerulonephritis or systemic lupus erythematosus before the treatment with prednisolone was essentially the
same as in those with essential hypertension. Exogenous glucocorticoid eliminated the circadian BP rhythm.

Circadian Rhythm of BP and HR in Patients with Primary Aldosteronism

As shown in Figure 3D, the pattern of circadian rhythm of BP and HR in patients with primary aldosteronism was essentially the same as that in patients with essential hypertension, but it was very different from that in patients with Cushing's syndrome. The changes in BP were well correlated with those of HR (SBP: $r = 0.70, p < 0.01$; DBP: $r = 0.78, p < 0.01$).

Comparison Between Daytime and Nighttime BP and HR

Table 1 shows the SBP, DBP, and HR averaged separately for daytime and nighttime periods. In untreated and treated subjects with essential hypertension and primary aldosteronism, SBP and DBP during the daytime were significantly higher than those for the nighttime. In subjects with pituitary or adrenal Cushing’s syndrome, whether or not they were treated with antihypertensive drugs, SBP and DBP during the nighttime were not significantly different from those during the daytime. Daytime HR in all groups was significantly higher than nighttime HR. The difference between daytime and nighttime HR in patients treated with combined antihypertensive drugs was significantly less than that in the other groups.

Discussion

In the present study, we have demonstrated that the circadian BP rhythm in patients with Cushing’s syndrome is very different from that in patients with essential hypertension or primary aldosteronism. The patients with Cushing’s syndrome were sometimes treated with several kinds of antihypertensive drugs because of their severe hypertension. However, the present study clearly demonstrates that a calcium antagonist in combination with diuretic, converting enzyme inhibitor, $\alpha$-blocker and $\beta$-blocker, or sympatholytic drug did not affect the pattern of circadian BP rhythm in patients with Cushing’s syndrome or essential hypertension. The disturbance of normal circadian BP rhythm has been reported in patients with malignant hypertension. In the present study, hypertension in Cushing’s syndrome, especially in adrenal Cushing’s syndrome, was severe. Thus, the disturbance of circadian rhythm of BP may have been the result of severe hypertension. However, the circadian BP rhythm in essential hypertensive patients whose averaged daytime SBP was similar to that in patients with adrenal Cushing’s syndrome remained undisturbed, suggesting that the BP level was not the sole factor contributing to its disturbance. Almost all the subjects examined in the present study had normal physical activity and undisturbed sleep. Taken together, these results suggest that the circadian BP rhythm in patients with Cushing’s syndrome (i.e., no nocturnal fall in BP and a peak BP level just before or after waking) may be peculiar to this syndrome. Furthermore, the present study demon-
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FIGURE 4. The influence of drugs on the circadian rhythm of SBP, DBP, and HR: that of nitrazepam in five patients with Cushing's syndrome (A) and that of prednisolone in six patients with chronic glomerulonephritis or systemic lupus erythematosus (B).

FIGURE 4. The influence of drugs on the circadian rhythm of SBP, DBP, and HR: that of nitrazepam in five patients with Cushing's syndrome (A) and that of prednisolone in six patients with chronic glomerulonephritis or systemic lupus erythematosus (B).

strated that exogenous glucocorticoid abolished the circadian BP rhythm in patients with chronic glomerulonephritis or systemic lupus erythematosus. This finding indicates that excess glucocorticoid, whether due to endogenous or exogenous glucocorticoid, affects the circadian BP rhythm.

Glucocorticoids alter the distribution of body fluid through their effect on vascular permeability. Excess circulating glucocorticoid may alter the fluid movement in response to a change in position; body fluid may shift excessively from extravascular to intravascular space when one shifts from a supine to a recumbent position during sleep, resulting in an increase in circulating volume, venous return, and cardiac output. Such an increase may raise the BP. This possibility is unlikely, since the elevation of BP from midnight to early morning was still observed in patients with Cushing's syndrome who remained in a recumbent position throughout the day.

In Cushing's syndrome, adrenal adenoma or the excessive production of ACTH from pituitary microadenoma causes excessive glucocorticoid secretion, and the ordinary circadian rhythm, if any, of the ACTH-cortisol system is disturbed. In the present study we also observed that the plasma cortisol level remained high throughout the day with little rhythm in patients with Cushing's syndrome (data not presented). Exogenous glucocorticoid also disturbs the ordinary hypothalamic-pituitary periodicity. The administration of glucocorticoid inhibits release of corticotropin-releasing factor and thus suppresses both the synthesis and release of ACTH. Such a disturbance of the hypothalamic-pituitary-adrenal axis may affect sympathetic nervous functions. For example, there is evidence that glucocorticoid modulates the synthesis of the sympathetic neurotransmitter and vascular response to catecholamine. Under normal circumstances steroid hormones are thought to pass the blood-brain barrier, and it has been reported that glucocorticoid acts centrally to increase sympathetic nerve activity. It has also been shown that adrenal catecholamine secretion is linked with ACTH and cortisol release.

Although the mechanism responsible for the nocturnal fall in BP is uncertain, withdrawal of sympathetic tone may play a major role, and the disturbance of the circadian rhythm of the ACTH-cortisol system in Cushing's syndrome, whether due to excess ACTH or cortisol, may disturb the circadian rhythm of the sympathetic nervous system, resulting in an altered circadian BP rhythm.

Many patients with Cushing's syndrome were reported to show some altered slow-wave sleep, suggesting a change in the quality of sleep in Cushing's syndrome. This was also confirmed in the present study (i.e., decreased slow-wave sleep and increased Stage 2 sleep). Changes in BP relating to

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sleep phases have been reported; therefore, altered sleep states in Cushing’s syndrome may affect the BP level at night. The elevation of BP during REM sleep is well established. In the present study, however, we found that the latency and sleep cycle of REM sleep was undisturbed. It is not yet known how increased time spent in Stage 2 sleep affects the BP level. In the present study, we also found that nitrazepam did not affect the BP pattern during night sleep in patients with Cushing’s syndrome. Nitrazepam increases the time spent in Stage 2 sleep and decreases the time spent in REM sleep. Therefore, it is difficult to conclude that the change in time spent in Stage 2 sleep or REM sleep (or both) alone affects the nocturnal levels of BP in Cushing’s syndrome. However, it is possible that the sleep state and the nocturnal behavior of BP, linking with each other, were affected by a common factor in Cushing’s syndrome of a differential pathogenesis.

Mineralocorticoid effects of excess glucocorticoid or excess production of aldosterone or deoxycorticosterone in Cushing’s syndrome do not appear to explain the altered circadian BP rhythm, since the pattern of BP changes in patients with primary aldosteronism was substantially the same as that in patients with essential hypertension. The circadian BP rhythm in patients with primary aldosteronism observed in the present study was very different from that reported by Tanaka et al. These earlier workers reported that BP reached its peak level around 20 to 24 hours. The reason for this difference is not clear.

The present results have demonstrated that the circadian BP rhythm is well correlated with that of HR in patients with essential hypertension or primary aldosteronism. The nocturnal fall of HR was retained in patients with Cushing’s syndrome, but that of BP was absent. Sleep bradycardia is due to increased parasympathetic activity but not to a decrease in sympathetic tone. This effect suggests that the circadian rhythm of parasympathetic tone remains unchanged in patients with Cushing’s syndrome; therefore, it is unlikely that the parasympathetic nervous system contributes to the nocturnal fall in BP.

The disturbance of the normal circadian BP rhythm has been reported in several pathophysiological conditions, such as pheochromocytoma, malignant hypertension, preeclampsia, and autonomic failure. The present results have demonstrated that the circadian BP rhythm is also disturbed in patients with Cushing’s syndrome. The available evidence suggests that physical activity is not of fundamental importance in determining the daily variations in BP that have been described. Although we cannot infer the existence of an inherent circadian BP rhythm from the results of the present study, it may be hypothesized that the circadian variation of BP is mediated at least in part by the hypothalamic-pituitary-adrenal axis through its action on the autonomic nervous system.

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*Recently we reported that ordinary circadian rhythm of BP was observed in patients with pheochromocytoma.


