24-Hour Blood Pressure Profile in Addison's Disease

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The purpose of this study was to evaluate the circadian blood pressure rhythmicity in patients with primary adrenal insufficiency. Ten newly diagnosed and untreated patients with Addison's disease, 17 addisonian patients (including the previous 10) following an adequate regimen of corticosteroid replacement therapy, and 15 healthy subjects as a control group were studied. Twenty-four–hour ambulatory blood pressure and heart rate were measured automatically every 30 min using a Takeda TM-2420 recorder. The runs test, used for detecting blood pressure diurnal rhythm, was compatible with a rhythm in 2 of 10 patients with untreated Addison's disease, in 13 of 17 patients with treated Addison's disease, and in 13 of 15 normals. Six of eight addisonian patients showing no evidence of blood pressure rhythm in the untreated state acquired circadian periodicity during therapy. An analysis of blood pressure readings by Fourier series with four harmonics showed that blood pressure mesor was lower in untreated than in treated addisonian and normal subjects ($P < .05$). The nocturnal fall was smaller for systolic and diastolic blood pressure in untreated than in treated addisonian and normal subjects ($P < .05$). Adrenocortical insufficiency is often characterized by loss of circadian blood pressure rhythm, and normal rhythm can be reestablished by replacement therapy. Lack of cortisol rhythm or persistent activation of the renin-angiotensin system and sympathetic tone may play a role in this phenomenon. Am J Hypertens 1994;7:1105–1109

KEY WORDS: **Addison's disease, ambulatory blood pressure, circadian rhythm.**

The presence of a circadian blood pressure rhythm has long been recognized in humans.[1,2] Various vasoactive hormones, eg, catecholamines, the renin-angiotensin-aldosterone system, and glucocorticoids, may influence this circadian periodicity, as their circulating levels tend to parallel the blood pressure rhythmicity.[3–6] Moreover, the rhythm is lost in cases of pathologic hypersecretion of these hormones, such as pheochromocytoma, renovascular hypertension, or Cushing's syndrome.[7,8] Scanty data are available on the 24-h blood pressure pattern in situations in which hormone secretion is chronically deficient. In this study, we present data on the day/night blood pressure changes in patients with adrenal insufficiency and compare them with those of a normotensive control population.

PATIENTS AND METHODS

Three groups of subjects, all hospitalized in the same institution, were studied: untreated addisonian, treated addisonian, and normotensive subjects. The first group included 10 patients (6 males and 4 females, aged 18 to 58 years) newly diagnosed as suffering from primary adrenocortical failure. The diagnosis of Addison's disease rested on typical clinical manifestations and laboratory data: high serum potassium values, low levels of plasma and urinary cor-

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tisol uninfluenced by exogenous ACTH administration, elevated levels of endogenous ACTH, and low plasma and urinary aldosterone levels in the face of high plasma renin activity (PRA). The second group (7 males and 10 females, aged 18 to 67 years), including the previous 10, consisted of 17 addisonian patients following an adequate regimen of steroid replacement therapy (duration, 1 to 17 years). Maintenance treatment consisted of orally administered cortisone acetate, 37.5 to 50 mg/day (25 mg at 08:30 and 12.5 to 25 mg at 18:30) and fluorocortisone, 0.05 to 0.1 mg/day at 08:30. Adequacy of treatment was based on clinical well-being, normal serum electrolytes, and ACTH and PRA levels in the normal range. The samples for hormone blood measurements were obtained in all patients 3 h after the morning steroid dose, after 30 min of rest in an armchair. In all cases, both treated or untreated, adrenal insufficiency was of autoimmune origin. No neurologic, renal, hepatic, or cardiac diseases were present. As a control group, 15 sex-age–matched normotensive (blood pressure <140/90 mm Hg) subjects, admitted to the hospital for routine workup because of infertility problems, were studied. No endocrine or other diseases were subsequently found in any case.

Three to eight days after admittance to the hospital, all addisonian and normotensive patients underwent 24-h noninvasive ambulatory blood pressure and heart rate monitoring. The 24-h blood pressure recordings were obtained using a Takeda TM 2420 monitor (Osaka, Japan), which was calibrated against a mercury sphygmomanometer. The accuracy of both systolic and diastolic blood pressures measured with this equipment has been well documented and compared with sphygmomanometric and direct methods.[9,10] Subjects were fitted with the recorder on the morning of the day of the recording. The instrument was set to take readings at 30-min intervals for 24 h. All subjects included in the study had complete readings (48/48) over the 24-h period. During the monitoring, a written diary of physical and mental activities was kept. In this regard, no major differences were found among the three groups of subjects. The sleep span in darkness, lasting from 22:00 to 07:00, was recorded in patients' diaries and controlled by nursing personnel. Blood pressure readings of patients with sleep disturbances were discarded. In our laboratory all mean changes of ambulatory blood pressure from baseline to repeat recording, ie, 24-h systolic blood pressure, 24-h diastolic blood pressure, and day-night difference for systolic and diastolic blood pressure, are ≤2 mm Hg; these data are based on two 24-h blood pressure monitoring studies at least 3 months apart in 20 normotensive subjects. Twenty-four–hour blood pressure reproducibility was also studied in seven of our treated addisonian patients over a 3-month period and was within the same limit. For ethical reasons repeat blood pressure ambulatory recording in untreated addisonian subjects was not possible.

Statistical Analysis The data from 24-h blood pressure and heart rate profiles were analyzed with a computerized procedure that we developed on a Macintosh IIcx using an application of 4th Dimension 4.1.1 (ACIUS), a relational and programmable database. The runs test with a one-sided probability level of 1% was first used for detecting the existence of a circadian blood pressure and heart rate rhythm, in contrast to pure random variation.[11] Subjects showing a significant runs test for their systolic or diastolic blood pressure, or for both, were classified as having a circadian blood pressure rhythm. To describe the blood pressure profile, Fourier series with four harmonics were then fitted to readings over 24 h by weighted least-squares regression.[12] The 24-h blood pressure rhythm is characterized by the following parameters: 1) mesor (Midline Estimating Statistic of Rhythm): rhythm adjusted-mean; 2) amplitude: half of the difference between the maximum and the minimum blood pressure level predicted by the model; and 3) acrophase: the time of blood pressure maximum. Daytime and nighttime systolic and diastolic blood pressure and heart rate values were also calculated. We considered daytime hours as being from 07:00 to 22:59 and nighttime hours from 23:00 to 06:59. The nocturnal blood pressure and heart rate fall was defined as the difference between the average day and night values.

The statistical significance of differences between groups was assessed by the Wilcoxon ranked-sign test, or χ^2 test corrected with the continuity, as appropriate. Results are expressed as mean ± SEM. For this test a $P < .05$ was considered significant.

RESULTS

According to the runs-test, 2 of 10 patients (20%) with untreated Addison's disease showed a significant circadian rhythm for both systolic and diastolic blood pressure. The remaining eight patients did not have BP rhythmicity. In 13 of 17 patients (76%) with treated Addison's disease, the runs test was compatible with a significant rhythm for systolic blood pressure; in 10 patients a circadian rhythm was present for both systolic and diastolic blood pressure. Six of the eight addisonian patients showing no evidence of systolic blood pressure rhythm in the untreated state acquired circadian periodicity for both systolic and diastolic blood pressure during steroid replacement therapy. The two addisonian patients with circadian blood pressure rhythm before therapy maintained rhythmicity after steroid replacement. Figure 1 shows

a 24-h systolic blood pressure profile of a patient in whom the circadian rhythm, not detected in untreated state, was reestablished by treatment. Thirteen of 15 normotensive subjects (86%) showed a rhythm for systolic blood pressure, 11 had a rhythm only for diastolic, and 10 had a rhythm for both systolic and diastolic blood pressures. The χ^2 test revealed a significant difference in the proportions of patients with both systolic and diastolic rhythms of blood pressure between untreated and treated addisonian group ($\chi^2 = 7.34$, $P < .01$), as well as between the untreated addisonian and normal groups ($\chi^2 = 6.66$, $P < .01$), but not between the treated addisonian and normal groups.

The blood pressure and heart rate parameters are summarized in Table 1. Blood pressure mesor and amplitude were significantly lower in untreated than in treated addisonian and normotensive subjects ($P < .05$). Acrophase of the systolic blood pressure curves occurred in early afternoon in untreated addisonian and normal subjects, and in late morning in treated addisonian patients. Acrophase of the diastolic blood pressure curve occurred in the mid-morning in untreated and treated addisonian patients, and in early afternoon in normotensives. The nocturnal fall in systolic and diastolic blood pressures was significantly smaller in untreated addisonian than in treated addisonian and normotensive subjects ($P < .05$). No intergroup differences in heart rate nocturnal decline were found.

TABLE 1. BLOOD PRESSURE AND HEART RATE PARAMETERS OF UNTREATED ADDISONIAN (n = 10), TREATED ADDISONIAN (n = 17), AND NORMOTENSIVE (n =15) PATIENTS

	Untreated Addisonian Patients	Treated Addisonian Patients	Normotensive Patients
Mesor			
SBP (mm Hg)	101 ± 2*	116 ± 4	117 ± 2
DBP (mm Hg)	60 ± 2*	72 ± 3	74 ± 1
Nocturnal fall			
SBP (mm Hg)	8 ± 1*	15 ± 1	14 ± 1
DBP (mm Hg)	3 ± 1*	9 ± 1	8 ± 1
HR (beats/min)	11 ± 2	12 ± 1	13 ± 1
Amplitude			
SBP (mm Hg)	13 ± 1*	23 ± 4	24 ± 1
DBP (mm Hg)	8 ± 1*	16 ± 2	15 ± 1
Acrophase			
SBP (hh:mm)	14:45 ± 4:34	11:18 ± 3:04	15:12 ± 5:36
DBP (hh:mm)	10:55 ± 4:16	10:36 ± 3:20	16:16 ± 6:06

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

* $P < .05$ *untreated addisonian v treated addisonian and normotensive patients.*

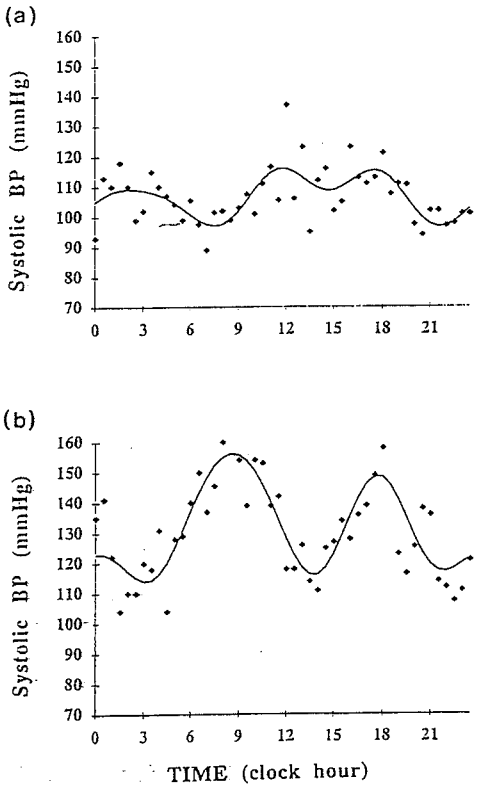

FIGURE 1. *Circadian profile of 24-h systolic blood pressure (BP) in an addisonian patient before* **(a)** *and after* **(b)** *steroid replacement treatment.*

DISCUSSION

The recent availability of portable automatic devices for noninvasive monitoring allows better assessment of the time-course of blood pressure variations around the clock and examination of rhythm characteristics.[13] A single cosine function may not adequately describe the circadian rhythm of blood pressure, and thus the use of Fourier analysis with k harmonics has recently been recommended.[12] Using such statistical methodology, our results in normotensive subjects confirm previous data from a much larger population.[14] At variance with normotensives, circadian rhythmicity was present in only 2 of 10 (20%) of our patients with untreated adrenal insufficiency. Addisonian patients are characterized by chronic deficient aldosterone and cortisol production, which leads to markedly high levels of renin-angiotensin II and ACTH, respectively, through the disruption of physiologic negative feedback control. While circadian rhythmicity of ACTH is reported to still be present in these patients,[4] no data are available about the persistence of a renin-angiotensin II circadian rhythm. Since either aldosterone or cortisol has been suggested to directly modulate diurnal blood pressure rhythm in humans,[15–17] the absence of circadian periodicity of these two steroids per se could account for the lack of blood pressure rhythmicity in our untreated addisonian patients. It cannot also be excluded that individuals with very low blood

pressure levels, such as these patients, are less likely to exhibit a circadian rhythm. Moreover, two other possible explanations can be proposed. One hypothesis is related to the probability that angiotensin II, which has been shown to be a major determinant of blood pressure in untreated Addison's disease,[18] is chronically elevated throughout both day and night. In fact, renin and angiotensin II normally rise during the night until midday and decrease afterwards until the nadir of the cycle in late evening. Thus, in the case of adrenal failure, hyperactivity of the renin-angiotensin system over 24 h could lead to persistent vasoconstriction. A similar mechanism has been suggested to explain the high frequency of blunted nocturnal decline among young essential hypertensive patients with high renin-sodium profiles.[19] A second possibility is again related to chronic salt and volume depletion, leading to increased sympathetic activity during the night. In fact, the effect of heightened adrenergic tone on blood pressure may not be apparent during the waking hours, when blood pressure is continually responding to changes in physical and psychologic demands. Nocturnal heart rate should be increased as a reflection of sympathetic tone. However, nocturnal heart rate day/night changes were similar in the groups of our untreated and normotensive addisonian patients.

After therapy, circadian blood pressure rhythm was reestablished in 6 of 8 patients with Addison's disease, confirming previous reports in patients with either primary or secondary adrenal insufficiency under replacement treatment.[20,21] The reappearance of rhythm was also associated with an increase of both blood pressure amplitude and nocturnal fall, approximately those of normal subjects. However, blood pressure acrophase of adequately treated addisonian patients does not correspond to that of normotensives, occurring earlier, ie, in the late morning. The timing of exogenously administered steroids and their relatively short half-life could play a role in this phenomenon.[22,23]

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