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Circulating adrenaline is not involved in the circadian blood pressure profile

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Background: Circadian changes in blood pressure are paralleled by analogous circadian changes in plasma catecholamines: blood pressure, plasma noradrenaline and adrenaline fall at night.

Objective: To determine whether adrenaline is a prerequisite for the nocturnal fall in blood pressure, the circadian blood pressure profile was studied in adrenalectomized subjects, lacking circulating adrenaline.

Subjects and methods: Ten adrenalectomized subjects and 10 healthy age-matched normotensive controls underwent 24-h non-invasive ambulatory blood pressure monitoring with the Oxford Medilog device. Measurements were taken every 15 min from 7.00 a.m. until 11.59 p.m and every 30 min from 12 midnight until 6.59 a.m. The nocturnal blood pressure fall was calculated for each subject.

Results: Mean \pm SD systolic blood pressure decreased at night by 13.2 ± 9.5 mmHg in the adrenalectomized and by 11.7 ± 7.3 mmHg (NS) in the control subjects. There was no significant difference between groups in the nocturnal diastolic blood pressure fall (14.4 ± 5.1 and 13.1 ± 5.2 mmHg, respectively). Systolic blood pressure decreased by >10 mmHg in five of the adrenalectomized and six of the control subjects. Diastolic blood pressure decreased by >10 mmHg in eight of the adrenalectomized and eight of the control subjects.

Conclusion: The normal nocturnal fall in blood pressure in adrenalectomized subjects indicates that circulating adrenaline is not required for a normal circadian blood pressure rhythm.

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Introduction

It has long been recognized that in most healthy subjects, blood pressure is higher during the day than at night. This biphasic diurnal blood pressure profile is probably the result of a complex interaction between endogenous factors like hormones, and autonomic nervous system and external factors like physical and mental activity and posture. External factors are probably most important in determining this circadian blood pressure rhythm [1], although these factors probably act by interfering with the sympatho-adrenomedullary system. Thus, during the night, low levels of physical and mental activity are accompanied by low activity of the sympatho-adrenomedullary system and this is considered to be responsible for the nocturnal fall in blood pressure

and the heart rate. In agreement with this view, plasma catecholamines, reflecting sympatho-adrenomedullary activity, exhibit a circadian oscillation that parallels that of blood pressure and the heart rate [2].

In patients with autonomic failure the nocturnal fall in blood pressure and plasma catecholamines is lost [3]. Conversely, some patients with a pheochromocytoma, with excessive levels of circulating catecholamines during both daytime and night-time, also lack a nocturnal fall in blood pressure [4]. So it is tempting to speculate that catecholamines affect the circadian blood pressure rhythm. To unravel the separate effects of noradrenaline and adrenaline on the circadian blood pressure profile, we examined 24-h blood pressure in adrenalectomized subjects lacking circulating adrenaline while having

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normal plasma noradrenaline levels. We hypothesized that if circulating adrenaline is a prerequisite for a normal fall in nocturnal blood pressure, we would not be able to demonstrate a diurnal blood pressure rhythm in subjects without circulating adrenaline.

Subjects and methods

The study was carried out in 10 subjects (mean \pm SD age 41 ± 12 years; two males, eight females) who had undergone bilateral adrenalectomy 2–14 years before the study. In nine of these subjects the primary disorder was Cushing's disease and in one subject this was an ectopic adrenocorticotrophic hormone (ACTH)-producing tumour. All subjects were taking cortisone-replacement therapy: cortisone-acetate at 37.5 mg/day ($n=9$) or hydrocortisone at 10 mg/day ($n=1$) and fludrocortisone at 0.1 mg/day ($n=10$). As further treatment, one patient was taking a β -blocker for hypertension and one subject was taking a conjugated oestrogen. In all adrenalectomized subjects, plasma adrenaline levels were undetectable (<0.04 nmol/l) while plasma noradrenaline levels were normal. Ten age-matched healthy subjects (aged 39 ± 11 years; three males, seven females) served as a control group. None of the control subjects was taking any medication.

All subjects underwent a 24-h ambulatory blood pressure monitoring (Oxford Medilog device; Oxford, UK) while continuing their normal daily activities and taking their regular drugs. Daily physical activity was not monitored except for the time in bed at night. The time the subjects went to bed varied from 10.30 p.m. to 12 midnight, and the time they awaked in the morning varied from 7.00 a.m. to 8.30 a.m.

Daytime was defined as 7.00 a.m. to 11.59 p.m. and night-time as 12.00 midnight to 6.59 a.m. So all subjects were in bed between 12.00 midnight and 6.59 a.m. Blood pressure and the heart rate were recorded every 15 min during the daytime and every 30 min during the night-time.

According to previously defined criteria, the raw blood pressure data were inspected and edited before analysis. Blood pressure values were excluded from analysis if systolic blood pressure was <50 mmHg, if diastolic blood pressure was <30 or >120 mmHg or if pulse pressure was >100 or <20 mmHg. In each subject, more than 80% of all readings were appropriate for analysis. The mean hourly blood pressure and heart rate values were calculated. Mean daytime, mean night-time and the mean difference between daytime and night-time blood pressure values were calculated. A nocturnal fall in blood pressure was defined as a decrease of >10 mmHg. In addition, in every subject, the night: day ratios for blood pressure and the heart rate were calculated from the mean daytime and night-time values. Changes in blood pressure or heart rate from day to night within a group were tested by the paired Student's *t*-test and differences between groups were tested by the unpaired Student's

t-test. Two-sided $P < 0.05$ were considered significant. Results are given as means \pm SD.

Results

Mean 24-h systolic blood pressure was not significantly different between adrenalectomized and control subjects (112 ± 7 and 110 ± 10 mmHg, respectively). Mean 24-h diastolic blood pressure was slightly higher in the adrenalectomized group (76 ± 6 mmHg) compared to the control group (66 ± 7 mmHg) but this difference was not significant. The mean 24-h heart rate was significantly higher in the adrenalectomized compared to the control group (81 ± 5 and 71 ± 8 beats/min, respectively; $P < 0.01$).

The time-course of both systolic and diastolic blood pressure over 24 h for both groups is shown in Fig. 1. Blood pressure and the heart rate decreased significantly during the night-time in both groups (Table 1). Systolic blood pressure decreased at night by 13.2 ± 9.5 mmHg in the adrenalectomized and by 11.7 ± 7.3 mmHg in the control subjects and this difference was not significant. There was also no significant difference between groups in the nocturnal fall in diastolic blood pressure (14.4 ± 5.1 mmHg in the adrenalectomized and 13.1 ± 5.2 mmHg in the control subjects).

Table 1. Mean daytime and night-time values and day: night ratios for blood pressure and heart rate in adrenalectomized (AEX) and control subjects.

	AEX	Controls
Daytime		
Systolic blood pressure (mmHg)	115 ± 8	113 ± 10
Diastolic blood pressure (mmHg)	76 ± 7	71 ± 7
Heart rate (beats/min)	$84 \pm 6^*$	75 ± 9
Night-time		
Systolic blood pressure (mmHg)	$102 \pm 8^{++}$	$102 \pm 12^{++}$
Diastolic blood pressure (mmHg)	$62 \pm 7^{+++}$	$57 \pm 9^{+++}$
Heart rate (beats/min)	$73 \pm 8^{+++}$	$64 \pm 9^{+++}$
Night: day ratio		
Systolic blood pressure	0.89 ± 0.08	0.90 ± 0.06
Diastolic blood pressure	0.81 ± 0.06	0.81 ± 0.08
Heart rate	0.86 ± 0.08	0.86 ± 0.05

Values are expressed as means \pm SD. * $P < 0.05$, versus control subjects; $^{++}P < 0.01$, $^{+++}P < 0.001$, versus daytime.

The individual nocturnal reductions in systolic and diastolic blood pressure are shown in Fig. 2. The nocturnal fall in systolic blood pressure was >10 mmHg in five adrenalectomized subjects and in six subjects in the control group. For diastolic blood pressure the corresponding numbers were eight adrenalectomized and eight control subjects. The number of subjects demonstrating a simultaneous nocturnal fall in both systolic and diastolic blood pressure of >10 mmHg also did not differ between the two groups of five

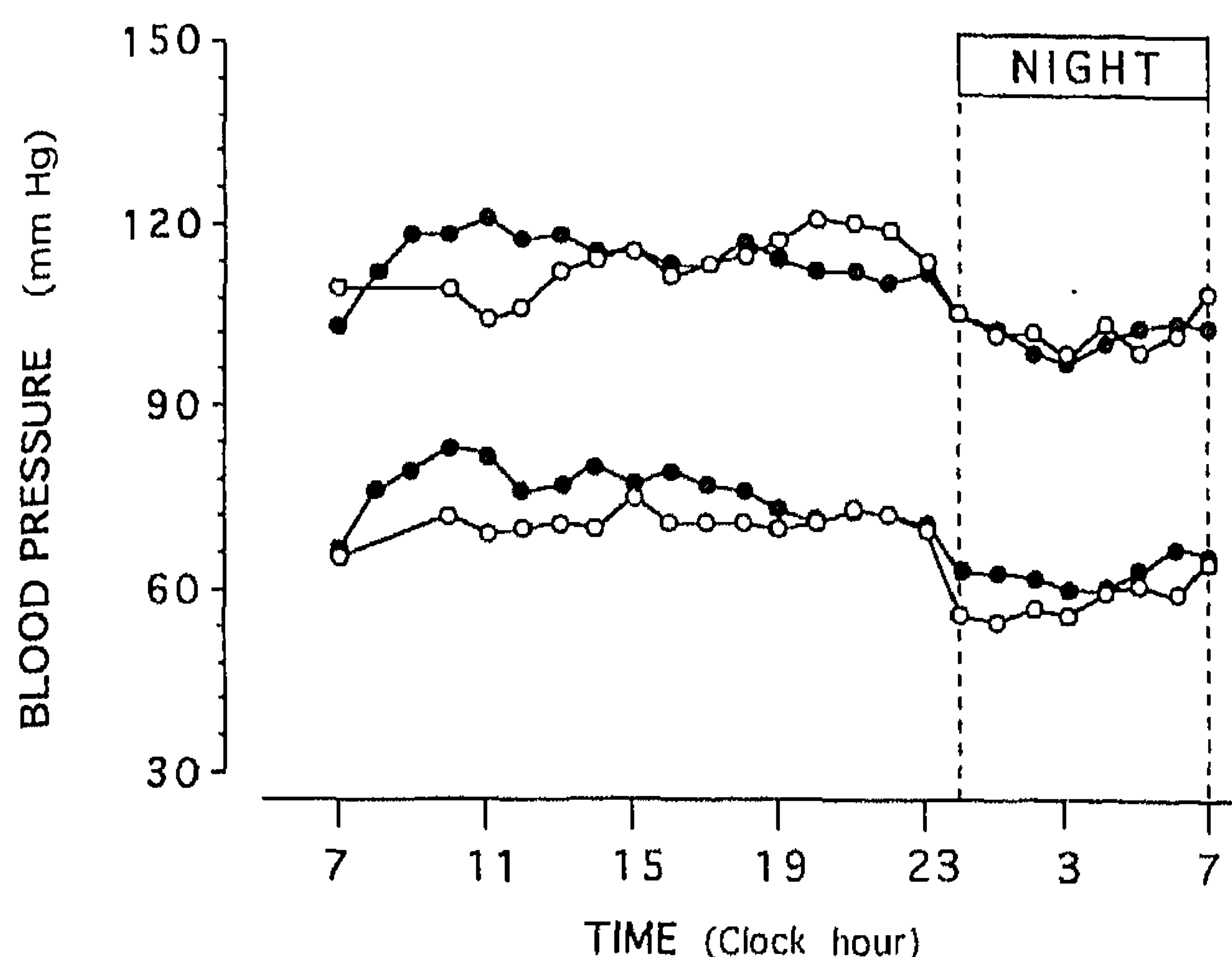


Fig. 1. Twenty-four-hour profile of systolic (upper points) and diastolic (lower points) blood pressure in adrenalectomized (●) and control subjects (○).

subjects, nor were the heart rate reductions different between groups (11.7 ± 7.2 and 10.3 ± 4.3 beats/min, respectively). The night : day blood pressure ratio did not differ between groups, and this applied to both systolic and diastolic blood pressure (Table 1).

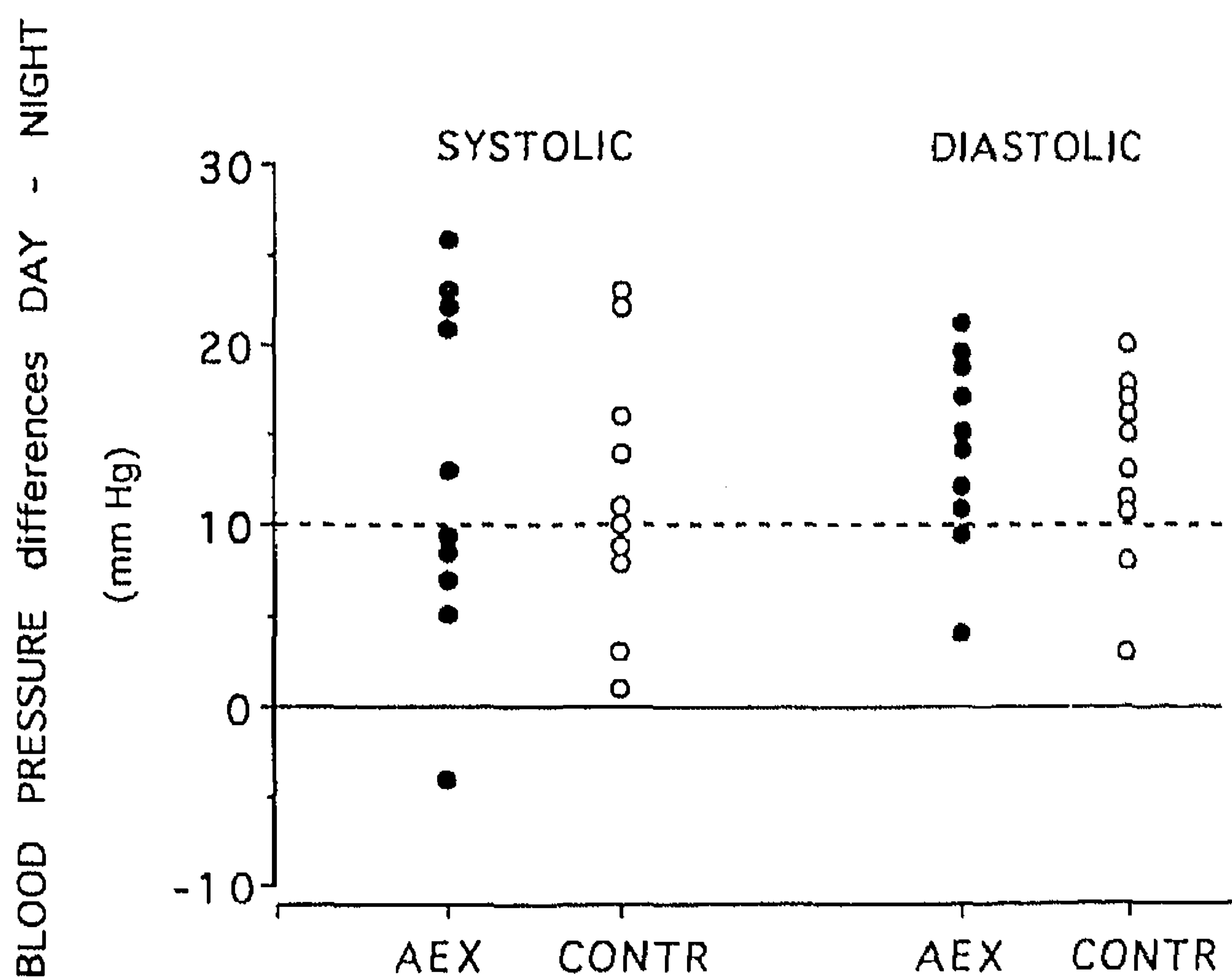


Fig. 2. Individual differences between daytime and nighttime blood pressure values in adrenalectomized (AEX) and control (CONTR) subjects.

Discussion

In this small group of patients who had undergone bilateral adrenalectomy, there was no difference in the number of subjects who had a nocturnal fall in both systolic and diastolic blood pressure compared to a control group of healthy subjects of similar age. In addition, there was no difference in the extent of blood pressure reduction between the two groups. Since plasma adrenaline levels were below the detection limit in all adrenalectomized subjects, these results imply that

circulating adrenaline is not a prerequisite for a normal diurnal blood pressure and heart rate profile.

A first explanation to be considered is that there is some extra-adrenal production of adrenaline. Adrenalectomized subjects are considered to be a model of adrenaline deficiency [5]. Nevertheless, both adrenaline and the enzyme necessary for the conversion of noradrenaline into adrenaline (phenylethanolamine-*N*-methyl-transferase) have been found in several organs [6]. Thus, despite the absence of circulating adrenaline, small amounts of non-circulating adrenaline may be present at vascular adrenoceptor sites.

An alternative explanation for the preserved circadian blood pressure profile is that aldosterone and cortisol are much more important than adrenaline for the circadian variation in blood pressure. Although corticosteroids preserve the vascular response for catecholamines [7] there is substantial evidence that they inhibit sympathoneural outflow [8]. Our patients were studied during replacement therapy with cortisone-acetate and fludrocortisone and these drugs may be pivotal for the preservation of the circadian blood pressure rhythm. Some supporting evidence has recently been reported: untreated patients with Addison's disease had no diurnal blood pressure rhythm but this was restored during replacement therapy with fludrocortisone and cortisone-acetate [9].

The most obvious explanation for the normal circadian blood pressure rhythm is the normally functioning sympathoneural system in these subjects. The sympathoneural system is a powerful regulator of the circulation and its activity is strongly related to physical activity and sleeping-waking cycle. After adrenalectomy, haemodynamic responses to several kinds of stress are preserved [10]. In the current study, sympathoneural activity was probably normal since these patients exhibited a normal nocturnal fall in the heart rate, suggesting that there was a normal decline in sympathoneural activity at night. Baseline plasma noradrenaline levels have also been shown to be normal in adrenalectomized patients [10] but plasma noradrenaline levels were not measured over 24 h in the present study. The strongest evidence that rhythmic sympathoneural activity is crucial in preserving the day-night blood pressure rhythm is the loss of this rhythm in patients with autonomic failure [3].

In the present study we did not use sophisticated methods for 24-h blood pressure analysis. Our simple question of whether circulating adrenaline is a prerequisite for a normal circadian blood pressure pattern can be answered by the methods of analysis that we used. We recognize, however, that we cannot exclude the possibility that there are subtle alterations in the 24-h blood pressure profile in these subjects. Despite these limitations, our data demonstrate that adrenalectomized subjects have a normal decline in night-time blood pressure, suggesting that circulating adrenaline is not a prerequisite for a normal circadian blood pressure pattern.

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