Circadian blood pressure profile in patients with Cushing’s syndrome before and after treatment

S. Zacharieva¹, M. Orbetzova², A. Stoynev³, R. Shigarminova¹, M. Yaneva¹, K. Kalinov³, E. Nachev¹, and A. Elenkova¹

¹Clinical Centre of Endocrinology and Gerontology; ²Department of Pathophysiology, Medical University; ³New Bulgarian University, Sofia, Bulgaria

ABSTRACT. The aim of the study was to evaluate the circadian blood pressure (BP) profiles in patients with two forms of Cushing’s syndrome, and to compare them to those in patients with essential hypertension. The study included 100 patients with Cushing’s syndrome (80 with pituitary adenomas and 20 with adrenal adenomas) and 40 with essential hypertension. Twenty-four-h ambulatory BP monitoring was performed before and after therapy. All 3 groups had similar office-, 24-h-, awake-, and sleep BP mean values. The awake-sleep differences between the patients with two forms of Cushing’s syndrome were similar. The night-time BP decline in the patients with Cushing’s disease, as well as in those with adrenal adenomas, was significantly lower than that in the patients with essential hypertension. In the patients with both forms of Cushing’s syndrome, there was a highly significant decline in the office and ambulatory BP levels after the treatment, and the awake-sleep systolic BP difference became significantly higher. The night-time diastolic BP decline was significantly higher after treatment in patients with adrenal adenomas and not-significantly higher in patients with Cushing’s disease. In the patients with Cushing’s disease, the duration of hypertension was greater, and lower percentage of normalized BP after treatment was observed in comparison with the patients with adrenal adenomas. The significant negative correlation between duration of the disease and extent of the night-time BP decline suggests that the ‘non-dipping’ profile is related not only to hypercortisolism itself but also to the severity of hypertension and duration of the disease.


INTRODUCTION

Ambulatory blood pressure monitoring (ABPM) is now widely used in clinical practice. Most studies have shown that the end-organ damage associated with hypertension is more strongly correlated with ambulatory than with manual blood pressure (BP) measurements (1). There is a progressive rise in risk of cardiovascular morbidity and mortality (stroke, myocardial infarction) with increasing levels of ambulatory BP (2). A diurnal variation in BP with falls in BP during sleep is well recognised. Some investigators suggest that night-time BP is more important than daytime BP in predicting outcome, particularly in individuals whose nocturnal (sleep) BP remains high (i.e., less than 10% lower than the day-time average – “non-dippers”) (3). In contrast, the Ohasama study found that the mean day-time ambulatory BP is a better predictor of mortality than night-time ambulatory BP (4). The absence of sleep-related reduction in BP has been shown in a number of pathological conditions including autonomic failure (5), pheochromocytoma (6), primary aldosteronism (7), diabetes mellitus and other secondary hypertensions (8).

The circadian pattern of arterial pressure is influenced by hormonal factors, such as the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axes, the renin-angiotensin-aldosterone system, opioids, and various vasoactives peptides. In rat strain (TGR) (mREN2) 27 (transgenic hypertensive rats), changes in the circadian pattern of ACTH-dependent steroids

Key-words: Ambulatory blood pressure monitoring, Cushing’s syndrome, essential hypertension, blood pressure.

Correspondence: Prof. S. Zacharieva, Clinical Centre of Endocrinology and Gerontology, 6, Damijan Gruve Str, 1303 Sofia, Bulgaria.
E-mail: zacharieva@uheg.medicalnet-bg.org
Accepted July 30, 2004.
are paralleled by changes in the circadian BP pattern, suggesting that the hypothalamic-pituitary-adrenal system plays a major role in modulating the circadian rhythm of BP (9). Several studies have demonstrated a loss of the normal BP decrease during the night-time sleep in endogenous hypercortisolism (10, 11). In addition, some studies have shown that the administration of exogenous glucocorticoids may be associated with the abolition of nocturnal fall in BP (12), but others have not confirmed these results (13).

Cortisol secretion follows a diurnal rhythm, with the levels being the lowest at the night and the highest between 08:00 and 09:00 h in the morning (14). The presence of diurnal BP variations that do not correspond exactly to those of cortisol levels in the means of cortisol rythm, as well as the data that both endogenous and exogenous glucocorticoïd excess may lead to loss of the normal circadian BP rhythm, gave us the ground to perform 24-h ABPM in patients with Cushing’s syndrome. The aim of the present study was to evaluate the circadian BP profiles in patients with two different pathogenic forms of Cushing’s syndrome, and to compare them to those in control subjects with essential hypertension. Furthermore, the effects of successful surgical therapy on circadian BP profiles were studied.

MATERIALS AND METHODS

Patients

We studied 100 patients (86 females and 14 males) referred to our clinic with a suspected diagnosis of Cushing’s syndrome and 40 patients (26 females and 14 males) with essential hypertension. Eighty of the patients with hypercortisolism had ACTH dependent Cushing’s syndrome due to pituitary adenomas and 20 patients had adrenal adenomas. The diagnosis of hypercortisolism was based on typical clinical profile, increased 24-h urinary free cortisol (UFC) excretion, high plasma cortisol levels, loss of plasma diurnal cortisol rhythm, and lack of suppression of plasma cortisol during low (2 mg) dose dexamethasone test. All patients with pituitary-dependent Cushing’s disease had detectable ACTH levels. This diagnosis was confirmed on the basis of histological findings after pituitary microsurgery or adrenal surgery.

Patients with ACTH independent Cushing’s syndrome had an undetectable level of ACTH and a lack of suppression of plasma cortisol during low (2 mg) and high (8 mg) dose dexamethasone test. In all patients adrenal masses were visualized by computed tomography. The cause of Cushing’s syndrome was verified histologically after adrenal surgery. The severity of the disease was estimated as the product of duration of the disease in months x UFC values (15).

Control subjects with essential hypertension were chosen from our ABPM database. These control hypertensive subjects had been referred to us for exclusion of endocrine hypertension and were found to have essential hypertension. Hypertension was confirmed by repeated BP measurements of systolic BP >140 mmHg and diastolic BP >90 mmHg. All patients were considered to have essential hypertension based on personal history, physical examination, and family history. The baseline evaluation included fundoscopy, electrocardiography, chest X-ray, standard laboratory tests (i.e. renal function tests), which enabled us to exclude secondary hypertension (for example, pheochromocytoma, renal vascular hypertension, Cushing’s syndrome, etc) to classify the severity of target organ involvement, and to determine if the patients had a clinical cardiovascular event.

The two groups with Cushing’s syndrome did not differ significantly from the essential hypertensive group in age, smoking habits, office BP and presence of left ventricular hypertrophy.

The patients gave informed consent to participate in this study. When possible, the use of antihypertensive agents was discontinued at least one week prior to study. The patients whose antihypertensive treatment had to be continued because of high blood pressure levels were shifted to calcium antagonists, or α-blockers 2 weeks before hospitalisation. The patients were kept on a normal diet and drank water ad libitum. No patient had a history of myocardial infarction, congestive heart failure, renal impairment or diabetes mellitus.

Office BP measurements

Office BP was measured in standard fashion with the patient sitting for 5 min. Systolic BP was taken as the first sound on deflation of the cuff (Korotkoff phase I), and diastolic BP was taken as the complete disappearance of Korotkoff sounds (Korotkoff phase V). At least two readings were taken and averaged to give the office BP used in this analysis.

24-h ABPM

Twenty-four-h ABPM was performed using Oscar monitors (Suntech Medical Instruments, USA). Systolic, diastolic, and mean BP as well as heart rate were measured at 15-min intervals during day-time (06:00-22:00 h) and 30-min intervals during night-time (22:00-06:00 h). Patients were instructed to go about their usual daily activities. All subjects kept a written diary of the activities and actual sleep times, and this was used to dichotomize the 24-h data into awake and sleep times for data analysis. Summary averages and BP loads were then calculated. Based on cross-sectional population studies, 24-h average BP loads were calculated using 130/80 mmHg thresholds. Awake BP loads were calculated using a threshold of 135/85 mmHg, and sleep BP loads were calculated using a threshold of 120/70 mmHg; (16, 17). Patients were categorized as becoming normotensive after surgery if their BP met the following criteria: 1) clinical BP <140/90 mmHg; 2) average 24-h ambulatory BP <130/80 mmHg.

Patients with fewer than 3 measurements per hour were not included in the study. ‘Non-dipping’ was defined in two ways. First, a ‘non-dipper’ profile was defined according to