Circadian Blood Pressure Profile in Patients with Active Cushing's Disease and after Long-term Cure

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Key words
- hypertension
- cardiovascular risk
- blood pressure dipping
- hypercortisolism
- treatment

Abstract

Hypertension is a major feature of Cushing's disease, with the attendant increase in the rate of cardiovascular events. The circadian blood pressure profile also impacts cardiovascular risk and a few studies have shown that patients with Cushing's syndrome do not present the expected nocturnal blood pressure decrease and, further, that this alteration persists in short-range disease remission. These studies were performed by conventional discontinuous ambulatory pressure monitoring, a technique not devoid of limitations. Aim of our study was the assessment of blood pressure and heart rate profile by beat-to-beat noninvasive monitoring in twelve patients with active Cushing's disease (9 women and 3 men, age 33.3 ± 2.36 years) and the assessment of its possible changes at short- (< 1 year) and long-term (2–3 years) follow-up after curative surgery. No nocturnal blood pressure dipping (i.e., decrease by 10% of daytime values) was observed in 50% of patients both during active hypercortisolism and within 1 year from surgery. Recovery of blood pressure dipping profile was detected at long-term follow-up in a minority of patients. Daytime heart rate was higher in patients with active Cushing's disease and decreased over time after cure. In conclusion, patients with Cushing's disease present absent nocturnal blood pressure dipping and abnormal heart rate values which do not resolve after short-term remission of hypercortisolism and show only partial improvement in the long run. These findings identify additional cardiovascular risk factors for patients cured of Cushing's disease.

Introduction

Cushing's disease is a rare endocrine disorder associated with considerable morbidity and mortality due to cardiovascular or cerebrovascular events, such as stroke, myocardial infarction, chronic heart failure, and pulmonary edema [1–4]. Mortality for patients cured of Cushing's disease, initially as high as 50% [1], now approaches that of the general population [4–7], but several features of hypercortisolism, most notably hypertension, diabetes and obesity, may persist notwithstanding the normalization of hypothalamo-pituitary-adrenal (HPA) function [2,8]. Indeed, patients with Cushing's disease appear to maintain an increased risk profile for cardiovascular events even after removal of the pituitary tumor [9] and in-depth evaluation of individual contributors to cardiovascular risk is needed in order to target therapeutic interventions.

Hypertension features as one of the main contributors to cardiovascular risk in terms both of absolute systolic and diastolic blood pressure levels and their variability [10–12]. Blood pressure variability is a complex phenomenon which includes short lasting changes induced by emotion and exercise as well as more prolonged fluctuations, such as those between wakefulness and sleep [13]. Blood pressure usually falls by 20–25% of daytime values during the night, the so-called "dipping" phenomenon, and this pattern is preserved in the majority of hypertensive patients. Approximately one third of hypertensives, however, fail to present a nocturnal blood pressure decrease, leading to the separation of patients into "dippers" and "nondippers" [11,14]. The reproducible [15] absence of blood pressure fall during nighttime is associated with an increased rate of adverse events, such as stroke [16], and with a greater degree of target organ damage, for example, left ventricular hypertrophy [17]. Further, independently from hypertension, other conditions may be associated with absence of dipping, for example, diabetes, obesity, autonomic dysfunction, and menopause [18–21].

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Table 1 Patient characteristics and antihypertensive medication

		Active phase		Within 1 year of surgery		Within 3 years of surgery	
Pt	age/ sex	Blood pressure status*	Medication	Blood pressure status*	Medication	Blood pressure status*	Medication
1	34/F	normal		normal		normal	
2	39/F	grade 1 hypertension	quinalapril 20 mg hydrochlorthiazide 12.5 mg	grade 1 hypertension	unchanged	grade 1 hypertension	unchanged
3	36/F	normal		normal		normal	
4	33/F	high normal		normal		normal	
5	45/F	grade 1 hypertension	losartan 50 mg	grade 1 hypertension	unchanged	grade 1 hypertension	unchanged
6	45/F	normal		normal		normal	
7	22/M	grade 1 hypertension	nifedipine 20 mg	grade 1 hypertension	lacidipine 4 mg atenolol 25 mg	grade 1 hypertension	atenolol 25 mg
8	27/F	grade 1 hypertension	cilazapril 5 mg	grade 1 hypertension	cilazapril 5 mg amlodipine 5 mg	grade 1 hypertension	fosinopril 10 mg
9	38/F	high normal		normal		normal	
10	34/M	grade 1 hypertension	no therapy	normal		normal	
11	28/F	normal		normal		normal	
12	19/M	high normal		normal		normal	

*Blood pressure status defined according to the 2003 Guidelines of the European Society of Cardiology [28]
Patients 1–5 were tested with Portapres at short-term follow-up only

Past studies of circadian blood pressure profile in patients with Cushing's syndrome, both endogenous and exogenous, revealed a high proportion of "nondippers" [22, 23], thus pointing to flattened circadian profile as an adjunctive cardiovascular risk factor. These studies, however, were performed using single, discontinuous noninvasive ambulatory blood pressure monitoring which, although widely used for clinical purposes, is subject to considerable intra-individual variability and does not allow unequivocal classification of dipping status [15, 24, 25].

From the abovementioned, it appears that evaluation of 24-hour blood pressure profiles in patients with Cushing's disease by more reliable techniques is necessary to definitively establish day-night blood pressure changes in these patients. Further, reassessment of circadian blood pressure profiles after curative surgery may provide further information not only on the causal role of hypercortisolism in the altered nocturnal blood pressure fall but also on the contribution of persistent hemodynamic alterations to residual cardiovascular risk in patients cured of Cushing's disease. The aim of our study was to precisely define circadian blood pressure and heart rate profile via computer-assisted analysis of 24-hour noninvasive beat-by-beat ambulatory blood pressure recordings (Portapres device) in patients with Cushing's disease before and after correction of hypercortisolism. This analysis integrates more than 100000 blood pressure and heart rate values continuously recorded over the day and night and provides a detailed and reliable assessment of 24-hour blood pressure and heart rate variations [26].

Patients and Methods

We studied 12 patients with Cushing's disease (3 men, 9 women; mean age 33.3 ± 2.36 years, range 19–45 years). The diagnosis of Cushing's disease had been established by standard diagnostic criteria [27] and confirmed by pathology of specimens excised by transsphenoidal surgery. All patients were studied in the active phase of the disease and again within 1 year (median 5.4 months) from surgical remission of hypercortisolism [27]; 7 patients were restudied 1–3 years (median 15.8 months) after surgery. Five patients were hypertensives (142.0 ± 7.21/83.5 ± 4.97 mmHg) and 3 additional patients were classified as having high normal blood pressure (135.6 ± 4.3/73.7 ± 1.81 mmHg) [>120/80; < 140/90 mmHg] [28] (**Table 1**). Four patients were on antihypertensive medication before surgery; antihypertensive treatment was continued in all patients for 1 year after surgery and for 2 years at prolonged follow-up (**Table 1**). Six patients tested within 1 year from surgery were on steroid replacement therapy while steroids had been tapered off in all patients retested after 1–3 years. Three patients were obese (BMI 42.5–51.3 kg/m^2), 4 overweight (BMI 26.1–28.3 kg/m^2), and the remaining 5 normal weight during the active phase of disease. Body weight fell in all patients after surgery, most markedly in the three obese patients (BMI at last follow-up 33.7–38.9 kg/m^2).

Endocrine evaluation

Twenty-four hour free cortisol (UFC) excretion was measured by radioimmunoassay of collected urine by extraction with dichloromethane (Byk-Sangtec Diagnostica, Germany). Samples for plasma ACTH and serum cortisol were collected in the morning after an overnight fast and measured by immunometric assays (Liason, Nichols Institute Diagnostics, San Juan Capistrano USA). Normal ranges in our laboratory are 2–11 pmol/l (10–50 pg/ml) for ACTH, 138–690 nmol/l (5–25 μg/dl) for 9.00 h serum cortisol, and 27.6–220.5 nmol/24 h (10–80 μg/24 h) for UFC.

Plasma samples for estimation of plasma renin activity and aldosterone concentrations were collected after overnight resting (clinostatism) and again after two hours of upright position (orthostatism). Both hormones were assayed by radioimmunoassay (Technogenetics, Cassina Dé Pecchi, Italy). Normal ranges for renin and aldosterone, in clino- and orthostatism, are 0.2–2 ng/ml/h and 1.5–5 ng/ml/h, and 277–4160 nmol/l (10–150 ng/l) and 830–8880 nmol/l (30–320 ng/l), respectively. Plasma samples for norepinephrine and epinephrine assays were collected after an overnight fast in nonstressed conditions, extracted with allumin and hormones assayed by HPLC. Normal ranges are 460–3000 nmol/l (78–521 ng/l) for norepinephrine and 55–1070 nmol/l (10–196 ng/l) for epinephrine.

Table 2 Blood pressure and heart rate circadian profile obtained with Portapres in patients with Cushing's disease before and after surgery

	Active disease	Within 1 year of surgery		Within 3 years of surgery	
		Mean values	Mean Difference vs. active disease (95 % CI)	Mean values	Difference vs. active disease (95 % CI)
24 h mean values					
systolic BP (mmHg)	130.2 ± 5.28	109.2 ± 5.35*	−19.7 (−36.6; −5.3)	109.2 ± 5.42*	−24.3 (−38.1; −3.9)
diastolic BP (mmHg)	75.4 ± 3.04	64.7 ± 3.45*	−10.5 (−20.2; −1.2)	64.9 ± 3.62*	−13.3 (−20.8; −0.2)
heart rate (beats/min)	84.9 ± 2.40	83.3 ± 3.60	−1.6 (−10.5; 7.3)	75.9 ± 1.98	−9.0 (−16.4; −1.6)
day mean values					
systolic BP (mmHg)	133.2 ± 5.39	111.8 ± 5.63*	−19.7 (−37.6; −5.2)	113.2 ± 6.06*	−22.9 (−37.8; −2.1)
diastolic BP (mmHg)	77.2 ± 2.94	66.3 ± 3.55*	−10.6 (−20.41; −1.39)	67.4 ± 4.09*	−6.5 (−20.2; −0.6)
heart rate (beats/min)	90.2 ± 2.35	86.9 ± 3.68	−3.2 (−12.1; 5.7)	79.5 ± 2.32*	−10.7 (−18.4; −3.2)
night mean values					
systolic BP (mmHg)	119.6 ± 5.76	104.4 ± 5.81	−11.4 (−31.9; 1.5)	100.5 ± 4.77*	−23.5 (−36.8; −1.3)
diastolic BP (mmHg)	68.9 ± 4.04	61.9 ± 4.45	−4.7 (−19.2; 5.2)	59.4 ± 3.69*	−13.8 (−22.2; −2.3)
heart rate (beats/min)	66.8 ± 2.19	69.4 ± 4.61	3.9 (−5.7; 10.9)	67.1 ± 2.30	0.3 (−6.8; 7.4)
nondippers (% patients)	50 % (21.7; −79.3 %)§	50 % (21.7; −79.3 %)	0 (−40.0 %; 40.0 %)	28 % (5; −61.3 %)	22.0 (−17.6 %; 61.6 %)

*$p < 0.05$ vs. active disease; §95 % C.I. in parentheses

Portapres

Beat-to-beat finger blood pressure was monitored noninvasively through a Portapres model 2 device over 24 hours based on the arterial volume clamp method [26]. In brief, the device measures blood pressure through two small finger cuffs wrapped around the middle and ring fingers of the nondominant hand which are alternated every 30 minutes. The device includes a system capable of automatically correcting for changes in finger pressure induced by hand displacements during daily life activities, by measuring the hydrostatic height difference between the instrumented finger and the heart level. The height-corrected finger arterial pressure and the hydrostatic height signal were stored together. Several papers have shown that use of Portapres technology, and in the more commonly employed stationary Finapres device based on the same blood pressure measuring approach, provides a reliable assessment of blood pressure variations over 24 hours, including beat-by-beat changes [26, 29, 30]. Possible problems related to analysis of finger blood pressure signal, known to be affected by physiological pulse wave distortion and by the progressive reduction in mean arterial pressure from centre to periphery along the arterial tree, were taken into account by application of an *ad hoc* digital filter and by blood pressure correction algorithm [31, 32]. The average discrepancy between the mean of three repeated arm cuff auscultatory readings and the mean of 5-minute continuous finger BP recordings was < 5 mm Hg in all patients. Antihypertensive medications were interrupted 7 days prior to testing.

Patients were asked to observe the following standardized activities: 1) 60-minute walking in the morning; 2) 90-minute nap after lunch; 3) 30-minute cycling at 50 W in the afternoon; 4) sleep between 10 PM and 6 AM. All patients were examined as inpatients both before and after surgery and monitored by one investigator during portapres registration (A.M.). Patients were asked about their sleep pattern on the morning after and none referred significant disturbances in sleep. Informed consent to participate in the study was obtained from all patients. The study protocol was approved by our Institution's Ethical Committee.

Recordings were analyzed by a specialized software obtaining 24-hour, day (6:00 AM–10:00 PM) and night (10:00 PM–6:00 AM) mean systolic and diastolic blood pressures and 24-hour, day and night mean heart rates. Day-night blood pressure ratios were calculated according to the formula: (mean day blood pressure/mean night blood pressure) × 100 [17]; patients in whom nighttime values fell by at least 10 % of daytime values were classified "dippers" while those in whom blood pressure did not were classified "nondippers". Heart rate values were classified in quartiles established by Verdecchia et al. [33] and circadian heart rate rhythm became flattened with less than 10 % day-night heart rate decrease [33].

Statistical analysis

Comparisons of values recorded before and after surgery in the same patient were performed by Wilcoxon's paired rank test and significance adjusted with Bonferroni's correction for multiple comparisons. Ninety-five percent confidence intervals of the differences were calculated in order to obtain estimates of the difference [34]. Qualitative variables were compared by chi-squared test or Fisher's exact test, as appropriate. Linear regression analysis was performed to assess association between variables. Data are given as mean ± S.E.M. or percentage and 95 % confidence intervals [34]. Statistical significance was accepted for $p < 0.05$.

Results

Active disease

Average blood pressure and heart rate values in patients with Cushing's disease are shown in **Table 2**. The physiological nocturnal blood pressure fall was lost in half of the patients with active Cushing's disease. Representative examples of normal, hypertensive dipping and Cushing's normotensive nondipping individuals are shown in **Fig. 1**; mean 24-hour systolic blood pressure, diastolic blood pressure and heart rate profiles in all patients with Cushing's disease are shown in **Fig. 2**. Only 6 out of 12 patients qualified as "dippers" (**Fig. 3**). Mean 24-hour heart rate was in the highest quartile [33] in 9 out of 12 subjects reflecting increased daytime heart rate values (**Table 2**, **Fig. 2**) while the nocturnal heart rate decrease was preserved (mean day-night decrease 26.1 ± 2.36 %).

Not surprisingly, BMI was higher in nondippers compared with dippers (36.6 ± 4.66 vs. 24.7 ± 0.99 kg/m^2, 95 % C.I. 16.7; 7.2 kg/m^2, $p < 0.05$), independent of day or night blood pressure as no correlation between BMI and blood pressure was detected. Conversely, no clear changes in day-night blood pressure drop with

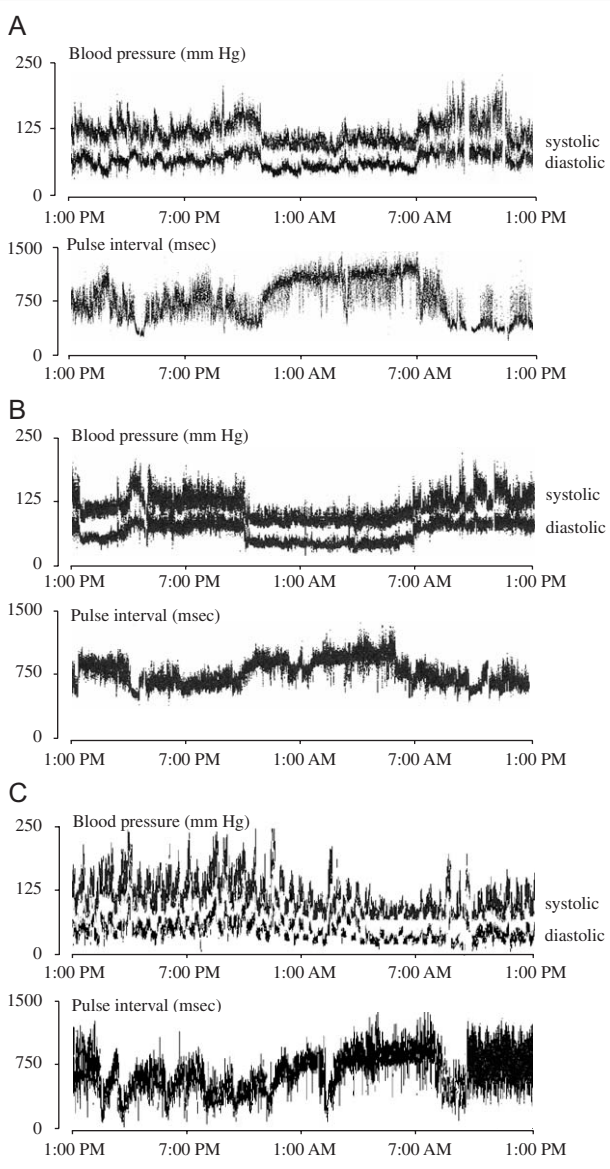

Fig. 1 Representative portapres recording of systolic and diastolic blood pressure (upper plot) and pulse interval (lower plot). **Panel A**: normal subject; **Panel B**: hypertensive patient with preserved day-night variation; **Panel C**: normotensive patient with Cushing's disease and absent nocturnal dipping. Blood pressure recording is depicted starting at 1:00 PM (13:00 h).

age were detected but this is probably due to the relatively young average age of our patients. No difference in day-night blood pressure fall was observed between the two genders (−14.9 ± 3.61/−9.6 ± 2.611 vs. −9.8 ± 5.2/−4.5 ± 6.24 mmHg for females and males, respectively; 95 C.I. −23.5; 13.3 mmHg for systolic blood pressure, −17.7; 7.5 mmHg for diastolic blood pressure, NS). The duration of disease was longer in hypertensive patients compared with normotensive patients although this difference did not reach statistical significance (7.1 ± 2.16 years vs. 4.2 ± 1.25 years, respectively; 8.1; −2.3 years, NS). Further stratification according to weight, gender or smoking failed to reveal significant differences in cardiovascular parameters.

Plasma renin activity increased modestly upon upright posture with resting values barely comprised in the normal range (**Table 3**). Aldosterone in resting and upright posture as well as catecholamines were comprised in the reference range for all subjects. No correlation was detected between hormonal levels and cardiovascular parameters, as well as with BMI.

Postsurgical evaluation

A significant decrease in average systolic, diastolic, and mean blood pressure was observed within 1 year of surgery in all patients (**Table 2**, ◉ **Fig. 2**). On average, 24-hour systolic blood pressure fell by 19.7 ± 5.62 mmHg and diastolic blood pressure by 10.5 ± 4.29 mmHg (reaching 85.5 and 87.2% of pretreatment values, respectively). Daytime blood pressure fell by 19.7 ± 5.51/10.6 ± 4.08 mmHg (achieving 85.6 and 87.0% of pretreatment values for systolic and diastolic values, respectively) while the nighttime blood pressure descent amounted to 11.4 ± 6.20/4.7 ± 5.81 mmHg, reaching 91.0 and 95.3% of pretreatment values for systolic and diastolic values, respectively. The decrease in both daytime and nighttime blood pressure was not sufficient to reinstate the physiological blood pressure fluctuation between day and night, and the percentage of nondippers remained unchanged at 50%. In detail, dipping status was recovered in 3 previously nondipping patients and lost in 3 patients who qualified as dippers in the active phase (◉ **Fig. 3**).

A more pronounced decrease in nighttime blood pressure was observed at prolonged follow-up (**Table 2**) with mean night values falling by 23.5 ± 5.39/13.8 ± 4.74 mmHg (reaching 82.4 and 83.3% of pretreatment; p = 0.07 vs. 1 year follow-up). Twenty-four hour and daytime blood pressures at prolonged follow-up were basically superimposable to earlier postsurgical measurements (24-hour blood pressure decrease: 24.3 ± 5.41/13.3 ± 3.36 mmHg; 82.6 and 83.8% of pretreatment values for systolic and diastolic blood pressure, respectively; daytime blood pressure decrease: 22.9 ± 6.48/12.0 ± 3.97 mmHg; 84.1 and 85.7% of pretreatment; NS vs. 1 year follow-up). On balance, this pattern allowed recovery of dipping profile in an additional nondipper patient thus lowering the percentage of nondippers at prolonged follow-up (28 vs. 50% in the active phase, p = 0.6 by Fisher's exact test; **Table 2**, ◉ **Fig. 3**).

A progressive reduction in 24-hour heart rate could be observed throughout follow-up (**Table 2**) although comparisons yielded marginal significance only at long-term evaluation (p = 0.056, ◉ **Fig. 2**). Overall, only 1 patient still fell in the highest heart rate quartile [33] at long-term follow-up. Stratification according to day-night phase revealed a significant decrease in daytime heart rate (12.1 ± 4.41 b/min at long-term follow-up; achieving 87.8% of pretreatment values, **Table 2**) while nighttime values were on the whole unchanged during postsurgical observation (102.9% of pretreatment values). Accordingly, the day-night heart rate difference was significantly smaller after surgery compared with pretreatment values (25.2 ± 3.65 b/min vs. 12.8 ± 2.35 b/min vs. 12.5 ± 1.89 b/min at pretreatment, first and second postsurgical evaluation, respectively, p < 0.01 vs. pretreatment for all comparisons) although still maintained within the expected 10% day-night decrease (15.5 ± 2.26% at last observation).

No significant changes in aldosterone and plasma renin activity in upright and recumbent position, and in epinephrine and norepinephrine concentrations were observed at short and long-term follow-up compared with values registered in the active phase (**Table 3**). Obviously, cortisol and ACTH levels decreased significantly after surgery. No clear association between changes in hormonal, BMI and cardiovascular parameters at follow-up could be observed by regression analysis.

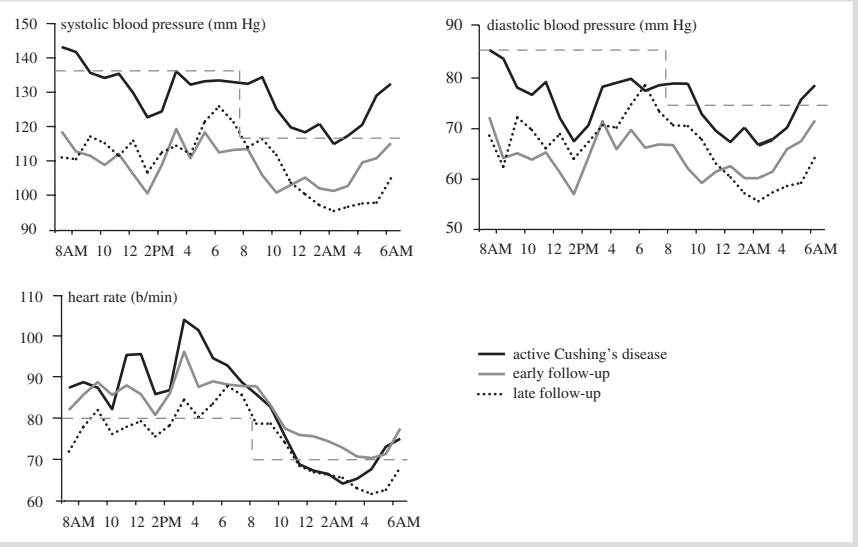

Fig. 2 Mean 24-hour blood pressure and heart rate profiles in patients with Cushing's disease before and after surgery. Mean systolic (upper left) and diastolic (upper right) blood pressures hourly values recorded in the active phase (black line), at early postoperative follow-up (grey line) and late postoperative follow-up (dotted black line) are shown. Slashed gray line indicates normal blood pressure reference levels: <135/85 for daytime hours, <115/75 for nighttime hours. Mean heart rate (below left) values follow the same legend. Reference data (<80 b/min for daytime hours, <70 b/min for nighttime hours) were taken from reference [33]. Blood pressure and heart rate recordings are depicted starting at 8:00 AM (8:00 h).

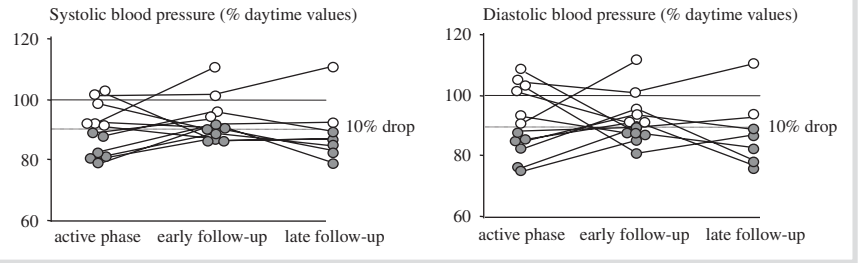

Fig. 3 Day-night changes in individual patients with Cushing's disease before and after surgery. Percent day-night systolic (left) and diastolic (right) blood pressure decrease in the active phase, at early postoperative follow-up and late postoperative follow-up. Dotted gray line indicates the expected 10% drop; grey circles indicate dippers, white circles indicate nondippers.

Table 3 Hormonal values in patients with Cushing's disease before and after surgery

	Active disease	1 year after surgery	1–3 years after surgery
plasma renin activity (ng/ml/h)			
resting (range 0.2–2)	0.4 ± 0.06	1.0 ± 0.43	0.4 ± 0.15
upright (range 1.5–5)	1.4 ± 0.52	2.6 ± 0.82	1.6 ± .036
plasma aldosterone (nmol/l)			
resting (range 277–4160)	978.6 ± 150.91	1167.7 ± 313.61	1848.6 ± 419.22
upright (range 830–8880)	2403.2 ± 488.06	3420.7 ± 135.88	3895.1 ± 137.61
catecholamines (nmol/l)			
norepinephrine (range 460–3000)	1035.4 ± 202.62	1486.0 ± 259.31	984.4 ± 118.70
epinephrine (range 55–1070)	102.6 ± 17.14	149.5 ± 16.42	125.5 ± 12.26

All comparisons are not significant

Discussion

Cardiovascular risk is known to depend on several factors, including clinical, biochemical, inherited, and behavioral elements. In this context, primary importance has been ascribed to elevated blood pressure, as hypertension represents one of the most important determinants of cardiovascular event rate [28]. Not only mean blood pressure levels but also blood pressure variations may contribute to cardiovascular risk. Indeed, blood pressure is characterized by a circadian pattern with higher levels during the daytime followed by a decline during the night. Subjects presenting an appropriate decrease in nighttime blood pressure (i.e., greater than 10% of daytime blood pressure) are classified as "dippers" while those who do not are defined "nondippers" [17]. Population studies have shown that the majority of hypertensive patients maintain a physiological variation pattern between day and night while the 24-hour blood pressure profile appears flattened in approximately one third [11, 14]. "Nondipper" hypertensives present greater left ventricular mass, faster progression of microalbuminuria and renal damage, higher number of silent ischemic/hemorragic cerebrovascular brain lesions, increased vascular stiffness, higher rate of cardiovascular events, and even increased cardiovascular mortality rate [12, 35–37], especially in subjects with reproducible alterations in the day-night blood pressure profile [15]. Nondipping occurs more frequently among diabetic and obese patients [18, 19] and dipping status may represent an independent risk factor for neuropathy, nephropathy, and vascular events in diabetic patients [38, 39].

Factors governing lack of night-time blood pressure dipping are as yet not fully understood, but inappropriate activation of the sympathetic nervous system [40], impaired natriuresis [41], and sleep apnea [42] may play a role. In addition, physiological changes in behavior such as sleep, rest, and physical activity may

contribute to absence of dipping [43]. Corticosteroids are known to influence blood pressure per se and are believed to play a role also in nocturnal dipping according to the evidence accrued in patients treated with these compounds. In fact, blunted systolic and diastolic blood pressure nighttime decrease has been observed in patients treated with glucocorticoids at pharmacological dosages [44] while replacement doses of steroids restore blood pressure rhythm in patients with Addison's disease who lack normal 24-hour blood pressure profiles [45,46].

In view of the above, and including the prominent role of nocturnal hypertension in patients presenting features common in Cushing's syndrome, such as obesity and diabetes, the evaluation of circadian blood pressure profile in hypercortisolemic patients is of considerable interest. Initial observations on small groups of patients with Cushing's syndrome reporting the flattening of the circadian blood pressure profile [22,47–49] have recently been confirmed in a large series of patients with pituitary or adrenal Cushing's syndrome [23]. This latter study evaluated circadian blood pressure profile at the diagnosis and after brief postsurgical follow-up using discontinuous noninvasive ambulatory blood pressure monitoring and observed a significantly higher proportion of "nondippers" among patients with Cushing's syndrome than that recorded in essential hypertensives. Blood pressure readings obtained from ambulatory blood pressure monitoring, however, may vary considerably in the same subject over time, and establishment of dipping status on the basis of a single monitoring has been questioned [15,24,25]. Measurement of blood pressure at closer intervals than those employed with conventional ambulatory monitoring, that is, on a beat-by-beat basis instead of every 15–30 minutes, is now available through noninvasive devices, such as Portapres, and is likely to yield more reliable results [26,30] as it is based on more than 100000 values rather than on approximately 90 readings. Our results using this method provide unequivocal evidence for the high prevalence of "nondipping" among patients with Cushing's disease, as the systolic and diastolic blood pressure decrease during the night fell short of the 10% threshold in over half of our patients. Short-term reevaluation after remission of hypercortisolism, that is, within 1 year from surgery, revealed that although average blood pressure fell consistently in all patients, the prevalence of nondippers remained high. In those patients evaluated after longer follow up (upto 3 years after surgery), a progressive recovery in nocturnal blood pressure dipping was observed in some individuals, leading to a slight amelioration in average dipping status. These findings indicate that mechanisms controlling nocturnal blood pressure dipping are severely affected by hypercortisolism and require a considerable period of time to normalize, if ever, after reestablishment of normal cortisol secretion.

A novel finding relates to elevated heart rate, a condition which has recently been shown to adversely affect cardiovascular risk [33,50]. We observed that patients with Cushing's disease often present increased 24-hour heart rates, due mainly to an increase in daytime heart rate. In contrast with blood pressure, increased heart rate values fell less dramatically after surgery and normalized only at prolonged follow-up. Past studies in patients with Cushing's syndrome had focused on the day-night heart rate decrease [22,47,49], which indeed is preserved in these patients, but did not report on absolute 24-hour and daytime heart rate values. The different behavior of diurnal and nocturnal heart rates may indicate an imbalance in neural cardiac reactivity involving sympathetic and parasympathetic activity during daytime but not during nighttime and deserve to be further investigated [33,50].

Successful treatment of Cushing's syndrome resolves around most signs and symptoms developed during the course of the disease [2,51,52] but some features of hypercortisolism may persist even after curative surgery/radiotherapy, such as elevated blood pressure values [8,53], altered glucose metabolism and insulin resistance [54,55], obesity [56] and GH deficiency [57], all leading to increased cardiovascular risk profile in the long-term [9]. The persistence of absence of nocturnal blood pressure dipping and increased 24-hour heart rates after remission of hypercortisolism over short term and, possibly, also long term, may contribute to persistent risk for cardiovascular events in patients cured from Cushing's disease. Treatment for patients recovering from Cushing's syndrome should therefore also be targeted to these alterations in blood pressure and heart rate profiles [50,58].

In conclusion, our data demonstrate that the majority of patients with active Cushing's disease present impaired circadian blood pressure and heart rate profiles. These alterations persist early after remission of hypercortisolism and appear to partially ameliorate only in the long-term. Thus, the absence of nocturnal blood pressure "dipping" represents an additional cardiovascular risk factor that may contribute to excess cardiovascular morbidity in the active phase of the disease and, possibly, also after remission of hypercortisolism.

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