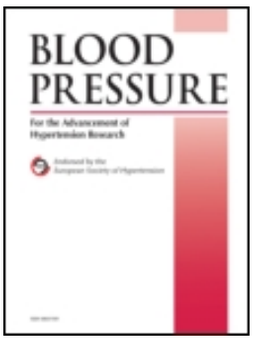

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Short-term Reproducibility of Nocturnal Non-dipping Pattern in Recently Diagnosed Essential Hypertensives

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Objective: To investigate in a selected population of patients with a recently diagnosed essential hypertension the short-term intrasubject variability of diurnal changes in blood pressure (BP). *Methods:* Two hundred and eight consecutive, recently diagnosed, never treated essential hypertensives (119 men, 89 women, 46 ± 12 years) underwent 24-h ambulatory BP monitoring (ABPM) twice within 3 weeks. Dipping pattern was defined as a reduction in average systolic and diastolic BP at night greater than 10% compared to average daytime values. *Results:* 177 subjects (85%) showed no change in their diurnal variations in BP. Of the 159 subjects who had a dipping pattern on first ABPM, 134 (90.6%) confirmed this type of profile on the second ABPM, while 15 (9.4%) showed a non-dipping pattern. Of the 59 subjects who had a non-dipping pattern on the first ABPM, 43 (72.2%) confirmed their initial profile on the second ABPM, while 16 (28.8%) did not. *Conclusion:* These findings indicate that short-term reproducibility of diurnal changes in BP in early phases of untreated essential hypertension, characterized by a large prevalence of dipping pattern, is overall satisfactory. However, our study underlines that also in this particularly selected population of hypertensives the definition of non-dipping status on the basis of a single ABPM remains unreliable in about one-third of patients. *Key words: ambulatory blood pressure monitoring, hypertension, non-dipping pattern, reproducibility.*

INTRODUCTION

In last two decades the increasing availability of 24-h ambulatory blood pressure monitoring (ABPM) has provided a large body of information about the diurnal blood pressure (BP) changes associated with the sleep–wake cycle [1–3]. The typical diurnal pattern in both normotensive and hypertensive subjects is characterized by a relevant parallel reduction in BP and heart rate during night sleep [4]. Some individuals show a small or even absent BP fall at night and they have been classified as non-dippers [5]. The absent or limited nocturnal fall in BP has been reported in several conditions, including secondary hypertension, sleep apnoea syndrome and diseases characterized by altered autonomic cardiovascular regulation [6–8]. Although the mechanisms of the non-dipping pattern are complex and not fully explored, it has been argued that patients are exposed to a greater haemodynamic load throughout the 24 h [9]. This may be associated with a higher risk of target organ damage, such as left ventricular hypertrophy, cerebral lacunae, carotid intima-media thickening, microalbuminuria and, consequently, of cardiac and cerebrovascular events [10, 11]. However, the clinical and prognostic significance of a blunted or abolished fall in nocturnal BP has not gone undisputed. Some recent cross-sectional studies failed to demonstrate significant differences in cardiac and extracardiac target organ damage between dipper and non-dipper hypertensives with similar 24-h average BP values [12, 13]. One of the major reasons for the inability to confer an undisputable clinical value to a single quantification of the day–night difference in BP is represented by the limited reproducibility of this phenomenon [14, 15]. Despite the potential clinical relevance of this issue only few studies have examined the reliability of nocturnal non-dipping status within hypertensive individuals. In the present study, we evaluated the short-term variability of the nocturnal BP fall, measured on two occasions over a 3-week period, in a selected population of never-treated patients with recently discovered essential hypertension.

METHODS

Patients

Two hundred and eight consecutive, never previously treated hypertensive patients referred for the first time to our outpatient clinic by their general practitioners were included in the study. They met the following inclusion criteria: (1) recent (<2 years) diagnosis of hypertension

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Table I. *Demographic and clinical characteristics of overall study population*

Parameter	Value
Number of subjects	208
Age (years)	46 ± 12
Gender (M/F)	119/89
Body mass index (kg/m^2)	25 ± 4
Current smokers	59/208
Clinic systolic BP (mmHg)	146 ± 13
Clinic diastolic BP (mmHg)	96 ± 8
Clinic heart rate (beats/min)	77 ± 11
Total cholesterol (mmol/l)	5.61 ± 1.06
Triglycerides (mmol/l)	1.47 ± 0.91
Glucose (mmol/l)	5.22 ± 0.67
Creatinine (μmol/l)	89 ± 9

Data are expressed as mean ± SD; BP, blood pressure.

(systolic BP, SBP ≥140 mmHg or diastolic BP, DBP ≥90 mmHg); (2) absence of secondary hypertension, congestive heart failure, previous myocardial infarction, cardiac valve diseases, history of coronary by-pass, stroke, diabetes mellitus, renal insufficiency; (3) conditions preventing technically adequate ABPM (e.g. atrial fibrillation and other major dysrhythmias). Patients gave their informed consent to participate in the study and in all subjects 24-h ABP was monitored twice within a 3-week period (range: 7–21 days). Routine blood chemistry and urine analysis according to a minimum work-up recommended by the current WHO/ISH guidelines were carried out in all patients and additional investigations performed, if necessary, on the basis of clinical ground.

Clinic BP measurement

BP was measured during the morning (between 10.00 and 12.00 h) in the outpatient clinic by a physician using a mercury sphygmomanometer (first and fifth phases of Koroktoff sounds taken as SBP and DBP, respectively) after the subject had rested for 5–10 min in the sitting position. Three measurements were taken at 1-min intervals, and the average used to define clinic SBP and DBP.

ABPM

Twenty-four-hour ABPMs were carried out on the non-dominant arm using a Spacelabs 90207 device (Spacelabs Inc. Richmond, Washington, USA) after validation of readings against a mercury sphygmomanometer by means of a Y tube, with the subject sitting for at least 10 min [16]. The device was set to obtain BP readings at 15-min intervals during the day and at 20-min intervals during the night. The daytime period was defined as the time interval between 07.00 and 23.00 h, and the night-time period as that between 23.00 and 07.00 h. In each patient, the time of application (±1 h), and the daily activity were the same for two ABPMs. The patients were asked to attend their usual daily activities, to keep still at the times of measurement, to note the occurrence of unusual events or of a poor night's sleep in a diary and to go to bed at about 23.00 h and to stay in bed until 07.00 h. The BP monitorings were always performed over a working day (Monday to Friday). Each ABPM dataset was first automatically scanned to remove artefactual readings according to preselected editing criteria. SBP readings >260 or <70 mmHg, DBP readings >150 or <40 mmHg, and pulse pressure readings >150 or <20 mmHg were automatically discarded. The recording was then analysed to obtain 24-h, daytime and night-time average SBP, DBP and heart rate. Nocturnal dipping was defined as a reduction in average SBP and DBP at night greater than 10% compared with average daytime values [11]. Each subject was classified into one of three groups according to the consistency of its dipping or non-dipping status at first and second ABPM. Group 1 = dipper on both two recordings; Group 2 = non-dipper on both two recordings; Group 3 = non-reproducible dipping or non-dipping status.

Statistical analysis

Values are expressed as means ± SD and per cent. The significance of pairwise differences was assessed using Student's paired *t*-test. The differences between the three groups were tested using ANOVA; $p < 0.05$ was considered statistically significant.

RESULTS

The study population consisted of 119 men and 89 women aged 46 ± 12 years (Table I). At baseline mean clinic BP was 146 ± 13/96 ± 8 mmHg (range 132–185 mmHg for SBP and 85–114 mmHg for DBP); mean 24-h ABP was 139 ± 11/89 ± 8 mmHg; mean daytime and night-time ABP were 145 ± 11/94 ± 8 mmHg and 124 ± 12/77 ± 9 mmHg. Clinic and average 24-h heart rate were 77 ± 11 beats/min and 77 ± 8 beats/min, respectively. A reduction in both clinic and ABP values (mean 24-h, daytime and night-time BP) during the second ABP recording was observed, but was only marginal and not significant compared to the first one. A highly significant correlation was found between average 24-h BP in the first and in the second ABPM ($r = 0.89$ for SBP and $r = 0.83$ for DBP, $p < 0.001$ for both).

Reproducibility of dipper and non-dipper profiles

On the first ABPM a dipping pattern was observed in 149 (74%) of 208 patients and a non-dipping pattern in 59

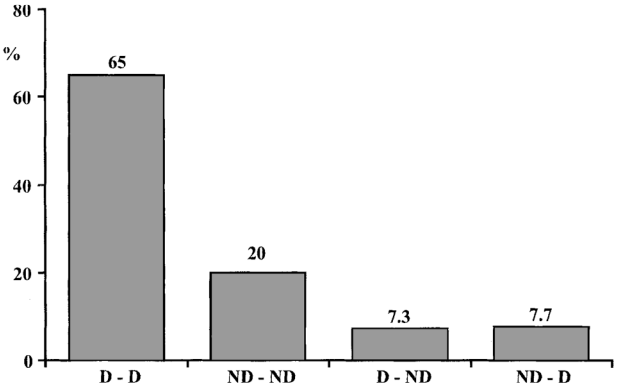

Fig. 1. Percentage of patients according to dipping status, defined by two ABPMs: dippers (DD), non-dippers (ND–ND), variable dippers (D–ND, ND–D).

patients (26%). Of the 149 patients who showed a dipping pattern on the first ABPM, 134 (91%) confirmed this type of pattern on the second ABPM, while 15 (9%) showed a non-dipping pattern. Of the 59 patients with a non-dipping pattern on the first ABPM, on the second ABPM this profile was confirmed in 43 (72%), while 16 (28%) had a dipping pattern. Therefore 177 patients had a concomitant BP nocturnal profile on both monitorings, 134 dippers (group 1), 43 non-dippers (group 2) whereas the remaining 31 patients had a variable profile (group 3) (Fig. 1).

Demographic and clinical characteristics in dippers and non-dippers

There were no significant differences in age, sex distribution, body mass index, heart rate and current smoking habit among subgroups classified according to circadian profile (Table II). Total serum cholesterol, glucose, triglycerides and creatinine concentrations were similar in the three groups. The mean 24-h SBP/DBP on first and second ABP monitoring was substantially superimposable among dippers, non-dippers and variable dippers. The mean daytime SBP was significantly higher in dippers than in non-dippers, whereas did not differ significantly in comparison to variable dippers in both ABP recordings. The mean daytime DBP was slightly but significantly higher in dippers than in two other groups only at second ABP recording. In both ABP recordings, SBP and DBP at night were significantly lower in dippers than in non-dippers.

DISCUSSION

The present study, carried out in a large sample of individuals during the early phase of the natural history of essential hypertension, shows that both absolute levels of 24-h, daytime and night-time ABP and diurnal changes in BP have a fair reproducibility over a short-term period. In fact, only a limited fraction of patients (<20%) changed their initial diurnal BP profile. However, this variability in circadian BP was significantly greater in patients

Table II. *Demographic characteristics and mean ABP values in dippers (Group I), non-dippers (Group II) and variable dippers (Group III)*

	I	II	III
Number of subjects	134	43	31
Age (years)	45 ± 12	48 ± 13	46 ± 11
Gender (M/F)	76/58	27/16	16/15
Body mass index (kg/m^2)	25 ± 4	26 ± 4	25 ± 3
Current smokers (%)	30	26	24
Heart rate (beats/min)	77 ± 12	79 ± 11	77 ± 10
T. cholesterol (mmol/l)	5.56 ± 1.01	5.59 ± 1.07	5.63 ± 1.1
Triglycerides (mmol/l)	1.45 ± 0.89	1.48 ± 0.96	1.46 ± 0.91
Glucose (mmol/l)	5.19 ± 0.59	5.25 ± 0.68	5.23 ± 0.72
Creatinine (micromol/l)	88 ± 10	89 ± 11	90 ± 9
First ABPM			
24-h ABP (mmHg)	138 ± 11/89 ± 8	138 ± 11/89 ± 8	139 ± 10/88 ± 8
Daytime ABP (mmHg)	146* ± 12/94 ± 9	141 ± 11/93 ± 9	144 ± 10/92 ± 8
Night-time ABP (mmHg)	122* ± 11/75* ± 8	131 ± 14/82 ± 8	127**** ± 13/78 ± 10
Second ABPM			
24-h ABP (mmHg)	137 ± 11/88 ± 8	136 ± 12/88 ± 8	138 ± 11/87 ± 9
Daytime ABP (mmHg)	144* ± 11/94** ± 9	139 ± 12/91 ± 9	142 ± 11/91**** ± 7
Night-time ABP (mmHg)	121* ± 10/75* ± 9	131 ± 12/81 ± 8	127*** ± 10/77 ± 9

Data are expressed as mean ± SD; ABP, ambulatory blood pressure.
* $p < 0.01$ I vs II; ** $p < 0.05$ I vs II; *** $p < 0.01$ III vs I; **** $p < 0.05$ III vs I.

classified at first ABPM as non-dippers (28%) than in dippers (9%). This finding underlines the fact that, also in a selected population including young and middle aged hypertensives, without concomitant confounding conditions such as diabetes mellitus, aging, renal failure, etc., the classification of non-dipper patients based on a single ABPM remains relatively unreliable. Several physiological and methodological reasons may explain the poor reproducibility of the circadian BP variation. The duration and quality of sleep are probably the most important physiological variables. Differences in the duration and depth of sleep may have a marked impact on the autonomic regulation of cardiovascular system during the night-time, leading to different changes in BP and heart rate. The definition of daytime and night-time periods is a critical point among the sources of poor reproducibility; a restrictive and fixed definitions of these intervals may exclude the morning and evening transitional periods during which a variable proportion of patients are actually awake or asleep [17, 18]. In our study all subjects were asked to go to bed and arise at a defined time (23.00 and 07.00 h). This approach identifies the night-time interval as the effective bed-rest period and allows to consider a larger number of BP values than that obtained with narrow fixed-clock intervals. To date, only few studies produced data on intrasubject variability in diurnal BP and all of them showed a poor reproducibility in nocturnal BP profile. Mochizuchi *et al*., assessing the day-to-day changes in ABP, found a similar variation in dipping and non-dipping status (28% and 31%) in untreated hypertensive outpatients [14]. In the subjects included in the Study on Ambulatory Monitoring of Pressure and Lisinopril Evaluation (SAMPLE), Omboni *et al*. demonstrated a 40% variability in the classification of dippers and non-dippers, after two recordings over a period of several months [15].

Dimsdale *et al*. found no reproducibility of nocturnal dipping status in a group of normotensives and unmedicated hypertensives; the patients, however, in one occasion were studied as outpatients and in the other one as inpatients in a clinical research ward [19]. More recently Manning *et al*. examined the long-term variability in nocturnal BP pattern and showed that 56% of their subjects did not change the dipping status whereas the remaning 44% had a variable pattern [20]. A notable result of the Manning's study was that the prevalence of patients with persistent non-dipping pattern was very low (3%). Our study, on the other hand, provides a new piece of information on short-term nocturnal BP variability in young, middle-aged uncomplicated hypertensives without any concomitant disease. Firstly, in this selected setting the majority of patients did not change their initial nocturnal BP pattern; secondly, the dipping profile, documented in the first ABPM, showed an excellent reproducibility (>90%); thirdly, less than one-third of the initially defined as non-dipper patients showed a reduction in night-time BP.

In conclusion, BP fall at night results from the interaction of several factors that may substantially vary and consequently influence its reproducibility over time. Our findings show that in a selected but clinically relevant hypertensive population the circadian BP variations were more reproducible than in previous studies, because an accurate methodological approach was used in order to minimize clinical and technical sources of short-term day-night BP variability. On the other hand, the study also underlines the need of caution in classifying patients as non-dippers on the basis of a single ABPM.

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