

# Cardiovascular changes in dipper and nondipper hypertension in perimenopausal women: time-dependent effects of antihypertensives

Wael Ragheb Refaie<sup>a</sup>, Ehsan Refaie<sup>b</sup>, Nagy Abd El Hady<sup>c</sup>, Salah Tantawy<sup>d</sup> and Ahmad Elewa<sup>e</sup>

Departments of <sup>a</sup>Cardiology, <sup>b</sup>Obstetric and Gynecology, <sup>c</sup>Internal Medicine, <sup>d</sup>Radiology and <sup>e</sup>Clinical Pathology, Mansoura Faculty of Medicine, Mansoura, Egypt

Correspondence to Wael Ragheb Refaie, Departments of Cardiology, Mansoura Faculty of Medicine, Mansoura, Egypt  
Tel: +01006077311; e-mail: refaie\_wael@yahoo.com

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## Background

The lack of a decrease in nocturnal blood pressure to up to 10% of the daytime measure is termed as nondipper (ND) hypertension. It is a cardiovascular (CV) risk factor with increased CV morbidity and accelerated target organ damage especially in women. The beneficial effect of restoring the ND state by administering antihypertensives (chronotherapy) at bedtime rather than on awakening is still debated.

## Objectives

The aim of this study was to determine the extent of ND hypertension and the magnitude of CV morbidities among perimenopausal women in comparison with an identical dipper group. The study also intended to determine the administration time-dependent effect on the ND state.

## Study design

The study included a cross-sectional part and a prospective randomized part.

## Patients and methods

One hundred and thirty perimenopausal women who were not known to be hypertensive, with an office blood pressure repeatedly exceeding 140/90 mmHg were included. After obtaining informed consents, complete history was taken and clinical examination was carried out. The included patients underwent 12-lead ECG and echocardiography, and the carotid intima-media thickness was measured. Besides the routine urine and blood analysis, analyses to obtain levels of lipids, HbA1-c, serum thyroid stimulating hormone, coagulation factors (factor VIII, fibrinogen), urinary albumin excretion, and C reactive protein were also carried out. Ambulatory blood pressure of all patients on a nonworking day was monitored. The studied patients were classified as dippers and NDs. The ND patients were randomly assigned to treatment with angiotensin receptor blockers (ARBs). Half of the ND patients received their dosage at bedtime and the others received the same dosage on awakening for 6 months, after which the ambulatory blood pressure was remeasured.

## Results

ND hypertension was detected in 61.5% of patients, its occurrence being significantly higher among women with hot flashes, those with postural hypotension, obese women, and among women with elevated HbA1-c, fibrinogen, cholesterol, C reactive protein and urinary albumin excretion levels. There was significant prolongation of the QTc interval and QT dispersion with a significant increase in the interventricular septal dimension and carotid artery intima-media thickness in the ND group. Disappearance of the ND phenomenon occurred in 80% of patients receiving therapy with ARBs at bedtime.

## Conclusion

ND hypertension is common among perimenopausal women, especially those with hot flashes, postural hypotension, and higher BMIs and HbA1-c levels, and is associated with many CV risk factors. Chronotherapy with ARBs at bedtime is more efficient in restoring the circadian rhythm of blood pressure compared with that on awakening.

## Keywords:

chronotherapy, dipper, nondipper

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## Introduction

Cardiovascular diseases (CVD) are the main cause of morbidity and mortality worldwide. Hypertension is one of the major traditional risk factors for CVD. Despite the availability of many groups of antihypertensives,

hypertension is well controlled only in 6–25% of patients [1].

In healthy as well as hypertensive individuals there is a diurnal variation in blood pressure (BP) levels, with a 10–20% decrease during the night. Patients without

a nocturnal (sleep) decline in BP to at least 10% of the daytime measure are referred to as nondippers (NDs) [2]. The classification of hypertension as dipper and ND is a relatively recent one dating back to the end of 1990, when Perloff and colleagues published their first seminal on awake ambulatory BP being a predictor of cardiovascular (CV) outcome [3–5].

There is substantial evidence indicating that night-time BP is a more powerful predictor of CV morbidity and mortality compared with conventional office or ambulatory daytime BP levels and that the ND pattern of hypertension is an added novel risk factor that has been associated with accelerated target organ damage (TOD) [6–9]. Although good BP control is one of the recommended targets in the management of hypertension [10], detection of the ND state is not universally applied and ambulatory BP monitoring (ABPM) is not even accepted as a clinical procedure in some countries [5]. Magnanini *et al.* [11] concluded that it is mandatory to use ABPM to evaluate, control, and guide therapeutic strategies in hypertension. Whether it is necessary to specify hypertension as dipper or ND by 24, 48 h, or 7 days of ABPM is not settled [5].

Chronotherapy is a new pharmacologic concept in which medications are delivered at a time and concentration that varies according to physiologic need during the dosing period. Although most types of CVDs follow a circadian (24-h) pattern [12], the use of chronotherapy for hypertension continues to lag despite many studies indicating that bedtime administration of conventional antihypertensive medication exerts better BP control and CVD risk reduction compared with the traditional approach of morning medication [13].

The ND phenomenon is more prevalent in hypertensive women who are also at a greater risk of TOD compared with ND hypertensive men, especially those under treatment with NSAIDs [14,15]. Past history of adverse pregnancy outcome and present history of hot flashes in hypertensive perimenopausal women involves a higher risk for ND hypertension and TOD [16,17].

### Objectives

The aim of this study was to identify the extent of ND hypertension among previously untreated perimenopausal women with repeated office BP of at least 140/90 mmHg and to elucidate the CV risk factors and comorbidities in a group of women with dipper hypertension versus an identical group of women with ND hypertension.

### Design

The study contains an observational cross-sectional part and a prospective comparative part.

### Subjects and methods

One hundred and thirty perimenopausal women with ages ranging from 46.5 to 54.5 years (not known to be hypertensive nor under previous treatment) presenting

at the Mansoura University Outpatient Clinics with nonspecific symptoms such as fatigability, weakness, occasional hot flushes, and oligo or amenorrhea, and with a repeated office BP measurement of at least 140/90 mmHg were recruited. Office BP in the sitting and standing positions was measured using a calibrated mercury sphygmomanometer with an appropriately sized cuff. Two BP measurements 5 min apart and the last reading were considered. After approval of the scientific committee and obtaining informed consent, the examined patients were subjected to complete clinical examination, stressing on history of previous adverse pregnancy outcome, hot flushes, and symptoms suggestive of CV, renal, and retinal affection. Detailed physical examination including estimation of BMI and waist circumference midway between the costal margin and iliac crest was carried out. CV examination including estimation of heart rate, arterial pulsation, edema, cardiac size, and cardiac bruit, as well as abdominal and fundoscope examination, were undertaken. The examined cases were classified as grade I and grade II hypertension according to the European Society of Hypertension, Society of Cardiology Guideline Committee [18].

### Exclusion criteria

Patients with suspected secondary hypertension, resistant hypertension, known or treated diabetes mellitus, collagen diseases, vasculitides, morbid obesity, depression, chronic obstructive pulmonary disease, sleep apnea syndrome, hepatic or renal dysfunction, or endocrinopathies were excluded.

The studied patients were subjected to 12-lead electrocardiograms, stressing on ischemic changes, ventricular dominance, arrhythmia, QTc intervals, and QT dispersion. Doppler echo cardiography stressing on measurement of interventricular septal diameter and interventricular septal thickness (IVST), and estimation of ventricular systolic and diastolic dysfunction was performed applying the criteria of the American Society of Echocardiography for left ventricular hypertrophy; left ventricular mass index (LVMI) greater than 104 g/m<sup>2</sup> was obtained [19]. LVM was calculated according to the procedure adopted by Devereux *et al.* [20] and was normalized for body surface area to obtain LVMI. The echo cardiographic procedures were conducted by an observer who was unaware of the dipper or nondipper state.

Carotid ultrasonography was performed for estimation of carotid intima-media thickness (CIMT) with stress on its diameter and presence or absence of atheromatous plaques and their characteristics. Ambulatory blood pressure was monitored for 24 h on a nonworking day; the intervals between measurements were 20 min during diurnal periods and 30 min during nocturnal periods [10].

All patients were subjected to 24-h urine collection and analysis for microalbuminuria; complete blood count, stressing on platelet count; and complementary analyses including estimation of levels of lipids (plasma cholesterol, triglycerides, HDL-c), HbA1-c, factor VIII, and C reactive protein (normally < 5 mg/l).

On analyzing the results from ABPM, 80 patients were found to be NDs and 50 patients were dippers. The ND patients were treated using angiotensin receptor blockers (ARBs; 160 mg valsartan); 40 patients received the medication at bedtime and the other 40 received the same dosage on awaking in the morning. The patients were followed up for 6 months; results of ABPM were rechecked and comparisons were made between patients receiving valsartan at bedtime and those receiving valsartan in the morning. CIMT values were also compared.

### Statistical analysis

Statistical analysis was performed using SPSS version 16 (SPSS Inc., Chicago, Illinois, USA). Qualitative data were presented as frequency and percentages. Quantitative data were examined using the Kalmogrov–Smirnov test to test for normal distribution of the data and, when parametric, were expressed as mean and SD. Student's *t*-test was used to compare differences in normally distributed quantitative data between the two groups. The Mann–Whitney *U*-test was used for comparison between two groups when the data were not normally distributed. A *P*-value less than 0.05 was considered significant.

### Results

ND hypertension was detected in 61.5% of the studied patients, its occurrence being significantly higher among women with hot flushes, adverse pregnancy outcomes, obese women, those with postural hypotension, fatty liver, elevated levels of HbA1-c, fibrinogen, cholesterol, and triglycerides, and those with increased microalbuminuria and CRP levels (Tables 1 and 2).

In the ND group, there was significant QTc prolongation and frequent QT dispersion. The CIMT revealed significant broadening in the ND group (Table 3), which

**Table 1 Clinical characteristics of the studied dipper and nondipper hypertensive groups**

Parameters	Dipper (50 patients)	Nondipper (80 patients)	<i>P</i>
Age (years)	49.7 ± 3.6	50.1 ± 2.1	0.476
BMI (kg/m <sup>2</sup> )	28.2 ± 1.9	30.1 ± 1.5	<0.001
WC (cm)	106.4 ± 14.6	112.2 ± 8.8	0.012
Fatty liver	15 patients (30%)	48 patients (60%)	<0.001
History of previous adverse pregnancy outcome	5 patients (10%)	32 patients (40%)	<0.001
Hot flushes	4 patients (8%)	36 patients (45%)	<0.001
Postural hypotension	5 patients (10%)	24 patients (30%)	0.007
Office SBP (mmHg)	168.8 ± 9.2	169.7 ± 8.1	0.571
Office DBP (mmHg)	104.01 ± 7.1	105.1 ± 5.2	0.349
ABPM morning SBP	158.7 ± 8.1	159.1 ± 9.1	0.794
ABPM morning DBP	100.02 ± 6.1	101.1 ± 4.1	0.270
ABPM evening SBP	140.1 ± 2.6	158.8 ± 3.1	<0.001
ABPM evening DBP	89.7 ± 0.3	103.1 ± 0.1	<0.001

ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; SBP, systolic blood pressure; WC, waist circumference.

was significantly reduced on treatment with valsartan and was further reduced by evening dosages (Tables 4 and 5). After 6 months of ARB treatment, there was significant restoration of the dipping state in 80% of the studied patients receiving valsartan at bedtime versus 30% of those treated with valsartan in the morning (Table 5).

### Discussion

Although the classification of hypertensive patients into dipper and ND groups is relatively recent [4,5], substantial evidence indicates that night-time hypertension is a more powerful predictor of CV morbidities and TOD [7–9].

**Table 2 Biochemical characteristics of the studied dipper and nondipper hypertensive groups**

Parameter	Dipper (50 patients)	Nondipper (80 patients)	<i>P</i>
HbA1-c (%)	6.1 ± 0.4	6.3 ± 0.6	0.024
TG (mg/dl)	140.8 ± 15.4	152.2 ± 20.8	<0.001
Cholesterol (mg/dl)	180.1 ± 15.4	195.7 ± 19.4	<0.001
HDL (mg/dl)	40.4 ± 8.6	36.4 ± 4.4	0.002
Fibrinogen (mg/dl)	324.34 ± 12.6	414.2 ± 18.1	<0.001
Excess factor VIII	10 cases (20%)	32 cases (40%)	0.018
CRP (IU)	3.5 ± 1.29	4.82 ± 1.5	<0.001
Microalbuminuria (mg/day)	20.8 ± 5.6	36.9 ± 6.1	<0.001
Platelet count (/cm)	180 000 ± 300.23	201 000 ± 119.9	<0.001
Uric acid (mg/dl)	5.1 ± 0.7	5.9 ± 0.8	<0.001

CRP, C reactive protein; HDL, high-density lipoprotein; TG, triglycerides.

**Table 3 Electrocardiographic, echocardiographic and carotid intima-media thickness among the studied groups**

Parameters	Dipper (50 patients)	Nondipper (80 patients)	<i>P</i>
Evidence of LV dominance	6 patients (12%)	12 patients (15%)	0.631
QTc (s; mean ± SD)	0.42 ± 0.11	0.44 ± 0.12	0.027
QTd	6 patients (12%)	24 patients (30%)	0.018
Evidence of LV diastolic dysfunction	10 patients (20%)	40 patients (40%)	0.018
Increased LVMI	6 patients (12%)	24 patients (30%)	0.018
CIMT (mm)	0.928 ± 0.09	1.01 ± 0.02	<0.001

CIMT, carotid artery intima-media thickness; LV, left ventricle; LVMI, left ventricular mass index.

**Table 4 Chronotherapy and restoration of the dipping state**

	Morning ARBs (40 cases)	Bedtime ARBs (40 cases)	<i>P</i>
Conversion to dipper	12 cases (30%)	32 cases (80%)	<0.001

ARBs, angiotensin receptor blockers.

**Table 5 Chronotherapy and carotid intima-media thickness**

	CIMT before	CIMT after	<i>P</i>
Morning ARBs (40 patients)	1.01 ± 0.02	1.01 ± 0.02	1
Bedtime ARBs (40 patients)	1.01 ± 0.01	0.9 ± 0.01	<0.001

ARBs, angiotensin receptor blockers; CIMT, carotid artery intima-media thickness.

Hypertension with a circadian nocturnal ND pattern seems to be relatively common. In the present randomized study, about two-third (61%) of the first-discovered grade I/II hypertensive perimenopausal women were found to be NDs. Sierra *et al.* [21] reported 40.2% of patients to be NDs and 13.4% to show a nocturnal rise in BP. Khromtsova [22] reported 56% of patients to be NDs. Mediavilla Garcoa *et al.* [23] reported that 49.6% of patients were NDs and 9.4% showed a nocturnal rise in BP. Gorostidi *et al.* [24] found the prevalence of the ND pattern to be 60% higher in high risk hypertensive patients, that is they support the recommendation of a wider use of ABPM.

In the present study, patients with associated conditions that lead to ND hypertension were excluded, for example those with diabetes mellitus [25], depression [26], sleep apnea syndrome [27], collagen disease, hemorrhagic vasculitis [28], chronic obstructive lung disease [29], and kidney disorders.

In Egypt hypertension is an endemic phenomenon (26.3%), being one of the most common risk factors for CVD. Hypertension in more than three-fourth of the patients is uncontrolled [30]. Cuspida *et al.* [31] reported that hypertension in only 6–25% of patients is controlled. Night-time hypertension was found to be a more powerful predictor of CV morbidity and mortality, which led to the consideration of the ND pattern of hypertension as an added novel risk factor [6]. Kulakov and Nasonova [32] found that ND hypertension is significantly higher in warm moist weather (cyclonic) like that in Egypt (in summer and spring months). Excessive intake of salts can also cause ND hypertension [33]. Egypt is one of the oriental countries with the population known to prefer food with a higher salt content. It may be speculated that the ND phenomenon is more frequent in Egypt because of its hot weather [32], high salt intake [33] and the habit of common use of pro hypertensive NSAIDS [14]. However this speculation awaits further confirmation.

In the present study, women with hot flushes and previous history of adverse pregnancy outcomes reported a high rate of ND hypertension. This is in accordance with studies by Gerrie Cor *et al.* [16], Ben-Ami *et al.* [34], and Hart *et al.* [17]. The control of BP in women with hot flushes needs identification of their nocturnal BP circadian pattern and specific chronotherapy.

Patients with orthostatism showed greater probability of nocturnal hypertension (Table 1). This is in agreement with the study by Carmona *et al.* [35] who concluded that orthostatism corresponds to a greater probability of nocturnal hypertension and thus selecting patients to undergo 24 h ABPM.

In the present study, a significant increase in micro-albuminuria was detected in the ND group (Table 2). This is in agreement with the study by Cobuz and Datch [36] who found that an early increase in nocturnal systolic blood pressure has key role in tracking the

progression of nephropathy. Davidson *et al.* [37] found that the rate of decline in glomerular filtration rate is an important factor in ND hypertension.

Factor VIII was increased in the ND group, and this is in accordance with the findings of Agorasti *et al.* [38]. Similarly, plasma fibrinogen was significantly higher in the ND group when compared with the dipper group. This is in accordance with the study by Hermida *et al.* [39], who found that patients with ND hypertension showed significantly higher levels of plasma fibrinogen throughout the year. The ND group in the present work revealed significant hyperlipidemia hypercoagulability, hyperuricemia, and increased levels of inflammatory marker, which are commonly associated with accelerated atherosclerosis and a tendency for hypertension emergencies.

In the present study, QTc was more prolonged with more evident QTd in the ND hypertension group compared with the dipper hypertension group. The ND hypertension state could predispose an individual to cardiac arrhythmia and sudden death [40]. Patients with ND hypertension had a significantly higher incidence of LVMI and left ventricular diastolic dysfunction attributed to HTN (ND) (Table 3), which is in agreement with the findings of Ersoylin *et al.* [41], who also found an increase in aortic root diameter, end diastolic IVST, and LVP wall thickness in patients with ND hypertension. The present findings also coincide with the findings of Cuspida *et al.* [1], who found that LVMI and IVST were significantly higher in the ND group.

Individuals with ND hypertension, especially women, are at a greater risk for TOD [15,40]. Hermida *et al.* [42] showed that patients with the ND pattern represent a risk factor for left ventricular hypertrophy. However, our results and many of the aforementioned studies are not in agreement with the studies by Gonzalez Quijada *et al.* [43] and Cuspida *et al.* [44] who reported no significant difference in LVM between dipper and ND groups and reported that ND-treated hypertensive patients did not have increased cardiac structural changes.

Our results of significant conversion of the ND state to the dipper state by nocturnal administration of ARBs is confirmatory of the findings of the recent MAPEC study [13], which reported that bedtime administration of conventional medications exert better BP control and CV risk reduction compared with the traditional approach of scheduling all medications in the morning. In the present study (Table 4), 80% of patients with ND hypertension became dippers on following the regimen of administration of ARBs at bedtime. Our results are in accordance with those of many other previous studies that revealed the beneficial effects of administering ARBs, angiotensin converting enzyme inhibitors, calcium channel blockers, and other antihypertensive drug therapies at bedtime in ND hypertensive patients [1,45,46]. Chronotherapy with valsartan improved BP during sleep and restored the diurnal rhythm in adequately controlled ND hypertensives with bedtime dosing [47]. Similarly, dosing with captopril at night was reported to restore the diurnal rhythm in

patients with adequately controlled ND hypertension [48].

## Conclusion

ND hypertension is frequent in perimenopausal women, especially the obese ones with hot flushes and/or postural hypotension. This is associated with ominous CV changes that may put the patients at a higher risk for CV disease. Chronotherapy with night dosing hypotensives is of greater value in ND patients. The use of ABPM strategies is needed to detect ND states of hypertension, and patients with ND hypertension should be meticulously investigated and monitored for CV dysfunctions.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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