Cent. Eur. J. Med. • 3(3) • 2008 • 279-286
DOI: 10.2478/s11536-008-0009-y

VERSITA

Central European Journal of **Medicine**

The effects of nocturnal dipping on cardiovascular outcomes and proteinuria in essential hypertensive patients

Research Article

Yusuf Selcoki[1*], Burak Uz[2], Nuket Baybek[3], Ali Akcay[3], Beyhan Eryonucu[1]

[1] *Fatih University, School of Medicine, Department of Cardiology, Ankara, Turkey*

[2] *Fatih University, School of Medicine, Department of Internal Medicine, Ankara, Turkey*

[3] *Fatih University, School of Medicine, Department of Nephrology, Ankara, Turkey*

Received 15 October 2007; Accepted 22 January 2008

Abstract: Individuals who do not have a 10% to 20% reduction in blood pressure (BP) during the night are known as 'nondippers'. Non-dipping patterns in hypertensive patients have been shown to be associated with an excess of target organ damage and other adverse outcomes. The present study was designed to investigate the relationship between nocturnal BP pattern, defined on the basis of the ambulatory blood pressure monitoring (ABPM) recording, and cardiac and renal target organ damage in a population of at least one year treated essential hypertensive subjects. The present analysis involved 123 patients with treated essential hypertension attending the outpatient clinic of our centre. Each patient was subjected to the following procedures: blood sampling for routine blood chemistry, spot urine for proteinuria, 24-hour periods of ABPM, and echocardiography. In the ABPM period, a dipping pattern was observed in 65 of the 123 patients, and a non-dipping pattern in 58 patients. Body mass index was higher in the non-dippers (26 ± 4 versus 28 ± 4, $p<0.05$). The proteinuria in spot urine was significantly higher in the non-dippers (10 ± 6 versus 24 ± 48, $p<0.03$). Left ventricular mass, interventricular septum thickness, posterior wall thickness and left ventricular systolic diameter were significantly higher in the non-dippers compared to the dippers. Left ventricular diastolic function was similar in non-dipper cases, except E- wave deceleration time. In treated essential hypertensives the blunted or absent nocturnal fall in blood pressure can be a strong predictor of cardiac and renal events. Hypertensive patients should be evaluated by ambulatory blood pressure monitoring. To prevent patients at risk for morbidity and mortality casualities as a result of hypertension, patients should be evaluated by ambulatory blood pressure monitoring. This method can be utilized for exacting future follow-ups with the patient.

Keywords: *Non-dipping • Essential hypertension • Target organ damage*

1. Introduction

There is mounting evidence that ambulatory blood pressure monitoring (ABPM) is superior to clinical blood pressure (BP) in the diagnosis and prognostic evaluation of hypertensive subjects, as it provides a large number of measurements taken during habitual daily activities and sleep [1,2].

With the use of the 24-hour ABPM, researchers have observed that BP usually fluctuates in a diurnal manner [3]. Diurnal refers to the daily variation of BP that is generally higher during the day than at night. Most people have an average night-time BP that is 10–20% lower than their average daytime BP [4]. Individuals with this normal night-time reduction are known as dippers, whereas the normal nocturnal fall of BP is diminished or blunted, the term "non-dipper" is applied.

The lack of nocturnal fall in BP has been related to an increase in target organ damage (TOD) and cardiovascular events. A number of studies have

* *E-mail: yussel1971@hotmail.com*

demonstrated that a non-dipping pattern in hypertensive individuals is associated with left ventricular hypertrophy [5], abnormalities in carotid structure [6], renal dysfunction [7], silent cerebrovascular disease [8], and is an independent predictor of cardiovascular events [9]. Other studies have failed to discover significant differences in cardiac and extra cardiac damage between night-time BP patterns among persons with essential hypertension. Several researchers have observed no significant differences in left ventricular hypertrophy (LVH) [10,11], left ventricular mass (LVM) [3,12], left ventricular mass index (LVMI) [3,13], carotid artery intimae to medial thickness [14,15], carotid artery plaques [15], cognitive functioning [16], microalbuminuria [17], and retinopathy [17].

A number of methodological problems, including different classification criteria for dippers and non-dippers, inappropriate selection of cases and controls, insufficient sample size, the effects of antihypertensive treatment and the limited reproducibility over time of nocturnal variations in BP, could explain conflicting conclusions obtained from a single nocturnal BP profile.

The mechanisms underlying the loss of the nocturnal reduction in BP are not completely understood. There is evidence to suggest the nondipping BP pattern is associated with autonomic nervous system activity impairment given that during the night individuals with a nondipping BP pattern have been found to have increased sympathetic nervous system activity [18], decreased parasympathetic nervous system activity [19], and have higher levels of epinephrine and norepinephrine when compared to individuals with a normal reduction in night-time BP [18]. However, there is also evidence to suggest that a nondipping BP profile may be associated with several demographic, physiological and psychosocial factors [20].

The present study was designed to investigate the relationship between nocturnal BP pattern defined on the basis of the ABPM recording, with cardiac and renal TOD in a population of hypertensives treated for at least one year.

2. Material and Methods

2.1. Study population and design

The present analysis involved 123 patients with treated essential hypertension attending the out-patient clinic of Fatih University, Department of Cardiology during a period of fifteen months (June 2006 – August 2007). All patients had been regularly followed-up for a period of at least one year. Patients with secondary hypertension, history or clinical evidence of congestive heart failure, previous myocardial infarction or coronary bypass, cardiac valve disease, stroke, diabetes mellitus or renal insufficiency were excluded. All patients were under anti-hypertensive therapy. Those who met the inclusion criteria and gave informed consent to participate in the study underwent the following procedures: (i) blood sampling for routine blood chemistry; (ii) spot urine for proteinuria; (iii) 24-h periods of ABPM; (iv) echocardiography. To avoid some of these potential methodological problems, in the present study we chose to define the night-time interval as the effective bed-rest period of 8 hours in order to consider a large number of BP recordings. The study protocol was approved by the ethics committees of the institutions involved.

2.2. Ambulatory Blood Pressure Monitoring (ABPM)

Twenty-four hour ABPMs were carried out on the non-dominant arm using a device (Delmar Reynolds, tracker NIBP 2) after validation of readings against a mercury sphygmomanometer by means of a Y tube. The device was set to obtain BP readings at 15 minute intervals during the day (07.00–23.00 h) and at 20 minute intervals during the night (23.00–07.00 h). The time of application (± 1 h) and the type of devices used for all patients was identical. The patients were instructed to attend their usual day-to-day activities but to keep with their measurement times. All subjects were asked to go to bed not later than 23.00 hours and to stay in bed until 07.00. The BP monitoring was habitually performed over a working day (Monday to Friday). Each ABPM dataset was first automatically scanned to remove artefactual readings according to preselected editing criteria. Systolic readings > 260 or < 70 mmHg and diastolic readings > 150 or < 40 mmHg were automatically discarded. The recording was then analyzed to obtain 24-hour daytime and nighttime averages for SBP, DBP and heart rates. According to the criterion of Verdecchia and colleagues, hypertensive patients with a nocturnal reduction in average daytime systolic BP and diastolic BP of less than 10% were classified as nondippers, while those with nighttime reduction of 10% or more were classified as dippers [21].

2.3. Echocardiography

2.3.1. Standard Echocardiography

In this study, we used a Toshiba corevision-pro machine with a 2.5-MHz probe. Echocardiography was performed while the patient was at rest, in the partial left decubitus position, with use of standard parasternal, short-axis, and apical views. Measurements of interventricular septal thickness (IVST), left ventricular end-diastolic dimension (LVIDd), left ventricular end-systolic dimension (LVIDs),

Table 1. Clinical and laboratory characteristics in dippers and non-dippers.

	Dippers (n = 65)	Non-dippers (n = 58)	p
Age (years)	59 ± 10	60 ± 8	0.35
Gender			
Males	20	22	NS
Females	45	36	NS
Body mass index (kg/m^2)	26 ± 4	28 ± 4	**0.04**
Smokers (%)	17.2	28.2	NS
Duration of hypertension (years)	7.6 ± 6	10 ± 8	0.07
Ambulatory measurements			
24-h SBP (mmHg)	123.23 ± 19.44	130.68 ± 20.52	0.14
24-h DBP (mmHg)	75.95 ± 7.22	77.80 ± 10.34	0.39
Daytime SBP (mmHg)	131.24 ± 9.36	131.94 ± 17.90	0.78
Daytime DBP (mmHg)	78.58 ± 8.12	79.01 ± 10.03	0.79
Night-time SBP (mmHg)	111.64 ± 8.51	126.54 ± 17.07	**<0.001**
Night-time DBP (mmHg)	64.90 ± 7.43	74.08 ± 10.19	**<0.001**
Serum biochemical markers			
Urea (mg/dl)	33 ± 11	32 ± 9	0.8
Creatinine (mg/dL)	0.8 ± 0.1	0.8 ± 0.2	0.08
Total cholesterol (mg/dL)	220 ± 44	212 ± 47	0.35
HDL cholesterol (mg/dL)	57 ± 14	58 ± 15	0.65
LDL cholesterol (mg/dL)	133 ± 36	123 ± 42	0.18
Triglycerides (mg/dL)	159 ± 116	157 ± 95	0.93
CRP (mg/L)	3.5 ± 3	4.8 ± 5	0.12
Protein in spot urine (mg/dL)	10 ± 6	24 ± 48	**0.03**

Except for those given as percentages, values are mean ± SD. BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein.

posterior wall thickness (PWT) and left atrial diameter were made according to the recommendations of the American Society of Echocardiography [22]. Left ventricular mass was calculated by the formula of Devereux and Reichek [23]. Relative wall thickness (RWT) was calculated as (2xPWT/LVIDd).

2.4. Conventional Doppler Echocardiography

Left ventricular diastolic function was assessed using transmitral doppler. The E and A filling velocities were measurable, as were E-wave deceleration time (EDT) and E/A ratio. The isovolumic relaxation time (IVRT) was also recorded from the apical 4-chamber view by simultaneous recording of the aortic and mitral flows [24].

2.5 Statistical analysis

Student's T test, Mann-Whitney-U and Chi-Square tests were used for statistical comparisons. SPSS (Statistical Package for the Social Sciences, version 10.0, SSPS, Inc, Chicago, IL, USA) software programme for Windows was used in personal computer. Results were presented as means ± S.E.M; P value < 0.05 was considered to be statistically significant.

3. Results

3.1. Demographic and biochemical results

The main clinical characteristics of the patients are given in Table 1. A total of 123 patients completed the study and had echocardiographic examinations of good technical quality. A dipping pattern was observed in 65 (52.8%) of the 123 patients, and a non-dipping pattern in 58 patients (47.2%). Of these patients, 81 (65%) were women and 42 (35%) men. Non-dippers tended to be older. Body mass index was higher in the non-dippers (26 ± 4 versus 28 ± 4, p<0.05). There were no significant differences in age, duration of hypertension and smoking habit in the two groups; in addition, serum total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, C-reactive protein (CRP), urea and creatinine levels were not significantly different among the groups.

Table 2. Echocardiographic data in dippers, non-dippers.

	Dippers (*n*=65)	Non-dippers (*n*=58)	*p*
LVIDd (cm)	4.4 ± 0.3	4.5 ± 0.3	0.15
LVIDs (cm)	2.7 ± 0.3	2.8 ± 0.26	**0.028**
IVST (cm)	0.97 ± 0.1	1.0 ± 0.1	**0.015**
PWT (cm)	0.96 ± 0.1	1.0 ± 0.1	**0.05**
Aortic root diameter (cm)	3.2 ± 0.2	3.2 ± 0.2	0.8
Left atrium diameter (cm)	3.4 ± 0.3	3.5 ± 0.4	0.25
LVM (g)	182 ± 41	200 ± 47	**0.02**
RWT	0.42 ± 0.045	0.43 ± 0.078	0.41
Ejection fraction (%)	65 ± 4	64 ± 0.2	0.19
Transmitral E wave (m/s)	0.74 ± 0.1	0.73 ± 0.1	0.7
Transmitral A wave (m/s)	0.81 ± 0.1	0.83 ± 0.1	0.4
EDT (ms)	185.42 ± 48.70	208.61 ± 51.23	**0.01**
IVRT (ms)	101.50 ± 21.97	107.05 ± 21.06	0.17

Except for those given as percentages, values are mean ± SD. LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; IVST, interventricular septum thickness in diastole; PWT, posterior wall thickness in diastole; LVM, left ventricular mass; RWT, relative wall thickness; EDT, E vave deceleration time; IVRT, isovolemic relaxation time.

3.2. BP nocturnal profile and cardiac structure and function

In the ABPM period, a dipping pattern was observed in 65 (52.8%) of the 123 patients, and a non-dipping pattern in 58 patients (47.2%). LVIDs, IVST, PWT, and LVM were significantly greater in non-dippers compared to dippers. LVIDd, aortic root diameter, left atrium diameter, RWT, and ejection fraction were similar in dippers and nondippers (Table 2).

Diastolic LV function was similar in non-dipper cases, except EDT. The transmitral E wave decreased (0.74 ± 0.1 vs 0.73 ± 0.1 m/s, P=0.7), the transmitral A wave increased (0.81 ± 0.1 vs 0.83 ± 0.1 m/s, P=0.4), and the transmitral EDT increased in non-dipper patients (185 ± 48 vs 208 ± 51 m/s, P=0.01). The isovolumic relaxation time increased (101 ± 21 vs 107 ± 21 m/s, P=0.17) in non-dipper patients.

3.3. Proteinuria

The proteinuria in spot urine was significantly higher in non-dipper patients (Table 1).

3.4. Pharmacological treatment

Pharmacological treatment regimens were similar in dipper and non-dipper patients. (Table 3). The compliance with pharmacological treatment was satisfactory in all/both patients; all patients reported taking the prescribed drugs regularly. The frequencies of using antihypertensive medicine categories were diuretics 10.8% vs 16.4%, angiotensin-converting enzyme inhibitor (ACEI) 24.6% vs 23.6, angiotensin receptor blocker (ARB) 46.2% vs 40.0%, calcium channel blocker (CCB) 23.1% vs 38.2, and beta-blocker (BB) 24.6% vs 27.3% respectively in dippers and non-dippers.

Table 3. Anti-hypertensive medications of study population.

	Dippers	Non-dippers	p
Diuretics	10.8%	16.4%	0.364
ACE inhibitors	24.6%	23.6%	0.901
Angiotensin II antagonists	46.2 %	40.0%	0.498
Calcium Antagonists	23.1 %	38.2%	0.072
Beta-blockers	24.6%	27.3%	0.740

4. Discussion

Cross-sectional and prospective data have shown that non-dippers have more target organ damage compared to dippers in normotensive and hypertensive subjects [25]. The results of the present study show that: (i) patients who had a fall in BP at night had more pronounced cardiac abnormalities compared to those with a dipper pattern; (ii) proteinuria in spot urine was higher in the non-dipper group than in the dipper group; (iii) patients in non-dipper groups tended to be older and had a higher BMI.

Since 1988, when the dipper/non-dipper classification was first introduced by O'Brien *et al.*, who, in a retrospective analysis, suggested that non-dipping hypertensive patients had a higher risk of stroke than the majority of patients with a dipping pattern [26], many studies evaluated the impact of a reduced decrease in nocturnal BP on cardiac and extracardiac TOD with discordant findings in both long-established

as well as recently diagnosed essential hypertensives. Some authors found that a decline less than 10% of daytime BP level (the standard threshold value used to define non-dippers) was associated with greater left ventricular structural and functional abnormalities, and renal dysfunction [5,7], while other investigators failed to demonstrate any significant differences in cardiac and vascular involvement between dippers and non-dippers [11,27]. These conflicting findings in the existing literature may partially reflect methodological problems. Patients who made up a large majority of the previous studies were on antihypertensive treatment for different intervals, this may have affected the relationship between BP and organ damage in a complex way. In addition, it is possible that the greater prevalence of LVH reported by some studies in non-dippers is a function of a higher cumulative 24-hour pressure load rather than the non-dipping phenomenon per se [28].

The most obvious explanation for the fall of pressure during sleep is a reduction of sympathetic nervous activity paralleling the change of arousal, and it is certainly true that many indexes of sympathetic activity, such as plasma catecholamines, heart rate, cardiac output, and peripheral resistance, are all lower [29]. In Cuspidi's study [11], the reduced nocturnal fall in BP was found in the majority of the whole study population (53%), and appeared particularly high in the group of refractory hypertensives (67%). These findings were in accordance with earlier reports of an increased prevalence of non-dippers among patients receiving antihypertensive therapy compared to untreated patients with recently diagnosed hypertension [30,31]. Different factors may explain this finding. In treated hypertensive patients non-dipping could be associated with the lack of therapeutical coverage for the 24-hour day. This complex phenomenon may reflect a predominance of pressure influences (*i.e*. angiotensin II, chatecolamines etc) over depressor ones (*i.e.* reduction of sympathetic nerve activity, an increase in vagal activity *etc*) that help to regulate BP at night [32].

By conventional Doppler echocardiography, we observed that the mitral E wave deceleration time was significantly prolonged in non-dipper patients with hypertension. The E wave deceleration time was characteristically prolonged in patients who had a relaxation abnormality, because it took longer for left atrial and ventricular pressures to equilibrate with a slower but continuous decrease in LV pressure [24,33].

An increased left ventricular mass and left ventricular mass index is a well known risk factor in hypertensive patients and can sometimes occur very early in the course of hypertension [34]. Compared to dipper hypertensives, non-dippers in our study showed a significant increase in their LVM. Aydin and colleagues suggested that, diastolic function impairment was more significant in non-dipper hypertensive patients than in dipper hypertensive patients [35]. However, conflicting data existed in the literature. Verdecchia et al. reported that, the changes in LVM showed a significant direct association with the changes in 24-hour systolic blood pressure [36]. Ferrrara *et al.* assessing LV structure and diastolic function in 123 patients with long-standing hypertension in whom antihypertensive treatment was discontinued for a period of 4 weeks, made note of any significant difference in left ventricle among dippers and non-dippers, suggesting that unfavorable consequences of non dipper status might be blunted by the duration of hypertension [37]. In a large sample of treated dipper and non-dipper essential hypertensive patients with different clinic BP control and prevalence of LVH shows that a reduced nocturnal fall in BP, established on the basis of a single ABPM, is not associated with more pronounced cardiac involvement. In fact, they found no difference in left ventricular size, systolic and diastolic function or prevalence of cardiac hypertrophy between patients with and without a normal fall in BP during the night [11]. These data were in agreement with several studies that failed to detect any significant difference between dipper and non-dipper hypertensive patients or found only a very mild impact of a blunted nocturnal BP reduction on cardiovascular characteristics [13,38].

In the present study, the proteinuria in spot urine was significantly higher in the non-dipper group. Timio *et al.* reported that the non-dippers had a faster rate of creatinine clearance decline than the dippers. Also the urinary protein excretion increase was higher in the non-dipper group than in the dipper group. A comparison of patients with hypertensive renal disease of over 3 years duration showed a 1.7-fold greater fall in creatinine and a 1.7-fold greater increase in the level of proteinuria in non-dippers as compared to dippers matched for such characteristics as age, sex, and office BP [39]. This phenomenon suggests that being a non-dipper is associated with a more rapid decline in renal function. We can suggest that the non-dipping pattern of ambulatory BP associated with a faster progression of renal insufficiency in hypertensives and that a proper nocturnal BP control is an additional aim of antihypertensive therapy.

There is evidence to suggest that individuals with essential hypertension and a non-dipping BP pattern have a disturbed circadian rhythm and standing position of natriuresis (excretion of excess urinary sodium) [40]. Uzu et al. [40] have postulated that among hypertensive individuals with a non-dipping BP pattern, daytime natriuresis is reduced leading to elevated mean arterial

pressure and increased natriuresis during the night. Further support of this hypothesis is the finding that diuretic therapy has been found to restore the nocturnal dipping BP pattern in hypertensive patients with a non-dipping BP pattern. Therefore, sodium restriction and diuretic therapy may have an additional therapeutic advantage of reducing the risk for cardiovascular complications by also restoring the dip in nighttime BP [41]. In our study, the usage of diuretic therapy was higher in non-dippers compared to dippers, but there was no significant difference.

A retrospective analysis of a large international database revealed the degree of BP non-dipping increased with age even after adjusting for sex, hypertension, and geographical location [4]. Contrary to the aforementioned study, Musialik *et al.* reported non-dipping BP patterns were more common among younger (22–45 years) hypertensive subjects when compared to older (65–79 years) hypertensive subjects in their study [42]. Multiple linear regression analysis showed that older age and decreased BMI were independent determinants of the non-dipper pattern. Environmental factors that may influence the circadian rhythm of BP include smoking, alcohol intake, and sodium intake [43,44]. In our study, non-dippers tended to be older. Body mass index was higher in the non-dippers. However, there were no significant differences in age, duration of hypertension and smoking in the two groups; in addition, serum total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, CRP, urea and creatinine levels were not significantly different in the groups.

The present study has some limitations. Firstly, microalbuminuria is known to be highly variable for detecting the renal damage, but we were unable to do it. Proteinuria in the spot urine was used and was measured only once in our patients. Secondly, further repetition of the ABPM sessions over a longer period of time may have provided an even more accurate classification of non-dipper subjects [45].

In conclusion, the non-dipper pattern of nocturnal BP is a strong predictor of cardiac events, and should be in older hypertensives. Furthermore, nocturnal BP appears to further predict the risk of hypertensive renal disease in older patients. If possible, hypertensive patients should be evaluated by ambulatory blood pressure monitoring in order to identify those patients at greater risk of morbidity and mortality; thus bypassing further complications and curtailing clinical problems through follow-up.

References

[1] Palatini P., Too much of a good thing? A critique of overemphasis of the use of ambulatory blood pressure monitoring in clinical practice, J. Hypertens., 2002, 20, 1917–1923

[2] Parati G., Mancia G., Ambulatory blood pressure monitoring in clinical practice, J. Hypertens., 2002, 20, 1925–1927

[3] Cicconetti P., Morelli S., De Serra C., Ciotti V., Chiarotti F., de Marle M.G., et al., Left ventricular mass in dippers and nondippers with newly diagnosed hypertension, Angiology, 2003, 54, 661–669

[4] Staessen J.A., Bieniaszewski L., O'Brien E., Gosse P., Hayashi H., Imai Y., et al., Nocturnal blood pressure fall on ambulatory monitoring in a large international database, The 'Ad Hoc' working group. Hypertension, 1997, 29, 30–39

[5] Verdecchia P., Schillaci G., Guerrieri M., Gatteschi C., Benemio G., Boldrini F., et al., Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension, Circulation, 1990, 81, 528–536

[6] Pierdomenico S.D., Lapenna D., Guglielmini L.D., Costantini F., Romano F., Schiavone C., et al., Arterial disease in dipper and nondipper hypertensive patients, Am. J. Hypertens., 1997, 10, 511–518

[7] Bianchi S., Bigazzi R., Baldari G., Sgherri G., Campese V.M., Diurnal variations of blood pressure and microalbuminuria in essential hypertension, Am J Hypertens 1994, 7, 23–29

[8] Shimada K., Kawamoto A., Matsubayashi K., Nishinaga M., Kimura S., Ozawa T., Diurnal blood pressure variations and silent cerebrovascular damage in elderly patients with hypertension, J. Hypertens., 1992, 10, 875–878

[9] Verdecchia P., Porcellati C., Schillaci G., Borgioni C., Ciucci A., Battistelli M., et al., Ambulatory blood pressure, An independent predictor of prognosis in essential hypertension, Hypertension, 1994, 24, 793–801

[10] Erdogan D., Gullu H., Caliskan M., Yildirim I., Baycan S., Ciftci O., et al., The influence of circadian blood pressure changes on aortic distensibility and left ventricular diastolic function in hypertensive individuals, Int. J. Card. Imaging, 2006, 22, 157–165

[11] Cuspidi C., Michev I., Meani S., Valerio C., Bertazzoli G., Magrini F., et al., Non-dipper treated hypertensive patients do not have increased cardiac structural alterations, Card. Ultrasound., 2003, 14,1-1

[12] Salvetti M., Muiesan M.L., Rizzoni D., Bettoni G.,

Monteduro C., Corbellini C., et al., Night time blood pressure and cardiovascular structure in a middle-aged general population in northern Italy: the Vobarno Study, J. Hum. Hypertens., 2001, 15, 879–85

[13] Grandi A.M., Broggi R., Jessula A., Laurita E., Cassinerio E., Piperno F., et al., Relation of extent of nocturnal blood pressure decrease to cardiovascular remodeling in never-treated patients with essential hypertension, Am. J. Cardiol., 2002, 89, 1193–1196

[14] Cuspidi C., Michev I., Meani S., Severgnini B., Fusi V., Corti C., et al., Reduced nocturnal fall in blood pressure, assessed by two ambulatory blood pressure monitorings and cardiac alterations in early phases of untreated essential hypertension, J. Hum. Hypertens., 2003, 17, 245–251

[15] Cuspidi C., Lonati L., Sampieri L., Macca G., Valagussa L., Zaro T., et al., Impact of nocturnal fall in blood pressure on early cardiovascular changes in essential hypertension, J. Hypertens., 1999, 17, 1339–1344

[16] Cicconetti P., Ciotti V., Monteforte G., Moise A., Chiarotti F., Piccirillo G., et al., Circadian blood pressure pattern and cognitive function in newly diagnosed older hypertensives, Blood Press., 2003, 12, 168–74

[17] Cuspidi C., Macca G., Sampieri L., Fusi V., Severgnini B., Michev I., et al., Target organ damage and non-dipping pattern defined by two sessions of ambulatory blood pressure monitoring in recently diagnosed essential hypertensive patients, J. Hypertens., 2001, 19, 1539–1545

[18] Sherwood A., Steffen P.R., Blumenthal J.A., Kuhn C., Hinderliter A.L., Nighttime blood pressure dipping: the role of the sympathetic nervous system, Am. J. Hypertens., 2002, 15, 111–118

[19] Nakano Y., Oshima T., Ozono R., Higashi Y., Sasaki S., Matsumoto T., et al., Non-dipper phenomenon in essential hypertension is related to blunted nocturnal rise and fall of sympatho-vagal nervous activity and progress in retinopathy, Auton Neurosci. 2001, 88, 181–186

[20] Routledge F., McFetridge-Durdle J., Nondipping blood pressure patterns among individuals with essential hypertension: a review of the literature, Eur. J. Cardiovasc. Nurs., 2007, 6, 9-26

[21] Verdecchia P., Porcellati C., Schillaci G., Borgioni C., Ciucci A., Battistelli M., et al., Ambulatory blood pressure, An independent predictor of prognosis in essential hypertension [published erratum appears in Hypertension 25:462]. Hypertension 1994, 24, 793-801

[22] Sahn D.J., DeMaria A., Kisslo J., Weyman A., Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements, Circulation, 1978, 58, 1072-1083

[23] Devereux R.B., Reichek N., Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method, Circulation, 1977, 55, 613-618

[24] Appleton C.P., Galloway J.M., Gonzalez M.S., Gaballa M., Basnight M.A., Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. Additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocity at atrial contraction, J. Am. Coll. Cardiol., 1993, 22, 1972-1982

[25] Izzedine H., Launay-Vacher V., Deray G., Abnormal blood pressure circadian rhythm: a target organ damage?, Int. J. Cardiol., 2006, 107, 343-349

[26] O'Brien E., Sheridan J., O'Malley K., Dippers and non-dippers, Lancet, 1988, 397

[27] Bjorklund K., Lind L., Andren B., Lithell H., The majority of nondipping men do not have increased cardiovascular risk: a population-based study, J. Hypertens., 2002, 20, 1501–1506

[28] Pickering T.G., James G.D., Determinants and consequences of the diurnal rhythm of blood pressure, Am. J. Hypertens., 1993, 6, 166–169

[29] Pickering T.G., Sleep, circadian rhythmas and cardiovascular disease, Cardiovasc Rev. Reports, 1980, 1, 37-47

[30] Leary A.C., Donnan P.T., MacDonald T.M., Murphy M.B., Physical activity is an independent predictor of the diurnal variation in blood pressure, J. Hypertens., 2000, 18, 405-410

[31] Hermida R.C., Calvo C., Ayala D.E., Mojon A., Lopez J.E., Relationship between physical activity and blood pressure in dipper and non-dipper hypertensive patients, J. Hypertens., 2002, 20, 1097-1104

[32] Mancia G., Zanchetti A., Cardiovascular regulation during sleep, In Oren J, Barnes CD (editors): Physiology in sleep. New York Academic Press, 1980, pp 1-55

[33] Oh J.K., Appleton C.P., Hatle L.K., Nishimura R.A., Seward J.B., Tajik A.J., The noninvasive assessment of left ventricular diastolic function with two-dimensional and Doppler echocardiography, J. Am. Soc. Echocardiogr., 1997, 10, 246-270

[34] Levy D., Garrison R.J., Savage D.D., Kannel W.B., Castelli W.P., Prognostic implications of

echocardiographically determined left ventricular mass in the Framingham Heart Study, N. Engl. J. Med., 1990, 322, 1561-1566

[35] Aydin M., Ozeren A., Bilge M., Atmaca H., Unalacak M., Dursun A., Elbey M.A., Left ventricular diastolic function and circadian variation of blood pressure in essential hypertension, Tex. Heart Inst. J., 2005, 32, 28-34

[36] Verdecchia P., Angeli F., Gattobigio R., Guerrieri M., Benemio G., Porcellati C., Does the reduction in systolic blood pressure alone explain the regression of left ventricular hypertrophy?, J. Hum. Hypertens., 2004, 18, 23-28

[37] Ferrara A.L., Pasanisi F., Crivaro M., Guida L., Palmieri V., Gaeta I., Iannuzzi R., Celentano A., Cardiovascular abnormalities in never treated hypertensives according to nondipper status, Am. J. Hypertens., 1998, 11, 1352-1357

[38] Schulte K.L., Lederwald K., Meyer-Sabellik M., Van Gemmeren D., Lenz T., Gotzen R., Relationship between ambulatory blood pressure, forearm vascular resistance and left ventricular mass in hypertensive and normotensive subjects, Am. J. Hypertens., 1993, 6, 786-793

[39] Timio M., Venanzi S., Lolli S., Lippi G., Verdura C., Monarca C., Guerrini E., Non-dipper hypertensive patients and progressive renal insufficiency, Clin. Nephrol., 1995, 43, 382-387

[40] Uzu T., Takeji M., Yamauchi A., Kimura G., Circadian rhythm and postural change in natriuresis in non-dipper type of essential hypertension, J. Hum. Hypertens., 2001, 15, 323–327

[41] Uzu T., Kimura G., Diuretics shift circadian rhythm of blood pressure from nondipper to dipper in essential hypertension, Circulation, 1999, 100, 1635–1638

[42] Musialik D., Kosicka T., Skoluda A., Boruczkowska A., Trojnarska O., Tykarski A., Twenty-four hour ambulatory blood pressure monitoring in young and elderly hypertensive subjects, J. Hum. Hypertens., 1998, 12, 641–642

[43] Mann S.J., James G.D., Wang R.S., Pickering T.G., Elevation of ambulatory systolic blood pressure in hypertensive smokers. A case control study, JAMA, 1991, 265, 2226–2228

[44] Harshfield G.A., Alpert B.S., Willey E.S., Somes G.W., Murphy J.K., Dupaul L.M., Race and gender influence ambulatory blood pressure patterns of adolescents, Hypertension, 1989, 14, 598–603

[45] Cuspidi C., Meani S., Salerno M., Valerio C., Fusi V., Severgnini B., Lonati L., Magrini F., Zanchetti A., Cardiovascular target organ damage in essential hypertensives with or without reproducible nocturnal fall in blood pressure, Journal of Hypertension., 2004 22, 273-280