

Echocardiographic indices of left ventricular hypertrophy and diastolic function in hypertensive patients with preserved LVEF classified as dippers and non-dippers

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Abstract

Introduction: Long-lasting arterial hypertension causes left ventricular hypertrophy (LVH) and impairs left ventricular diastolic function. Our aim was to compare echocardiographic parameters between hypertensive patients defined as dippers and non-dippers during ambulatory blood pressure (BP) monitoring.

Material and methods: We analysed 61 consecutive subjects with treated hypertension undergoing 24-h BP monitoring and transthoracic echocardiographic examination and included in the study patients with preserved left ventricular ejection fraction (EF \geq 50%). Echocardiographic and arterial pressure parameters were compared between the group classified as dippers ($n = 26$, 57 ± 13 years, 16 males) and non-dippers ($n = 35$, 60 ± 12 years, 24 males) according to present or absent decrease of BP during the night $> 10\%$. Echocardiographic data were compared between both groups and control subjects without hypertension.

Results: Dippers had lower average systolic, diastolic and mean arterial pressure during the night hours but did not differ according to the mean pressure calculated from a 24-hour period. All echocardiographic parameters were similar in dippers and non-dippers. All patients with arterial hypertension presented with larger dimension of both ventricles and left atrium, thicker left ventricular walls, higher LV mass and mass index and preserved EF and E/A ratio as compared with normotensive controls. Normal geometry, concentric remodeling and eccentric hypertrophy were similarly distributed in both groups. Concentric hypertrophy was more prevalent in non-dippers as compared to the dippers (71.4% vs. 38.5%, $p < 0.043$).

Conclusions: The concentric type of LVH is the prevalent pattern in non-dippers. Non-dipping blood pressure pattern may be responsible for the development of left ventricular concentric hypertrophy secondary to hypertension.

Key words: echocardiography, ambulatory blood pressure monitoring.

Introduction

Long-lasting, essential hypertension is usually associated with left ventricular hypertrophy (LVH) and impairs left ventricular diastolic function. Hypertension leads to different patterns of abnormal geometry of the left ventricle. The spectrum of cardiac morphological adaptation to high blood pressure encompasses concentric and eccentric hypertrophy. Eccentric

hypertrophy is characterized by a spherical left ventricle, increased stroke volume and low peripheral vascular resistance. Contrarily, most patients with concentric hypertrophy have an elliptic left ventricle, normal stroke volume and high peripheral vascular resistance [1]. Although any type of LVH increases the incidence of cardiovascular disease, the concentric type of left ventricular hypertrophy has been identified as the cardiac structural parameter that is most strongly related with cardiovascular risk [2, 3]. Blood pressure profile lacking sufficient physiological decrease during the night is believed to especially promote structural changes in the left ventricle [4]. The renin-angiotensin-aldosterone system (RAAS) is implicated in this process [5, 6]. In advanced stages the remodelling process causes diastolic dysfunction and organ damage, and poses an elevated risk of cardiovascular events [7, 8]. Moreover, left ventricular mass index (LVMI) is a significant predictor of left atrial enlargement (LAE), which is associated with increased cardiovascular hospitalization and mortality risk [9].

Ambulatory blood pressure (BP) values have been shown to have a better relationship to the left ventricular mass (LVM) of hypertensive patients with LVH than conventional office BP measurements [10]. Similarly, the regression of LVH associated with improved cardiovascular prognosis may be more closely correlated with reductions in ambulatory BP than office blood pressure [11-14]. Day-time and night-time blood pressure values and their changes due to treatment are related to each other [15], but the prognostic value of night-time blood pressure has been found superior [16]. Moreover, patients with a non-dipper circadian pattern of BP are at higher risk of micro- and macrovascular complications, such as cerebrovascular and cardiovascular complications, than individuals with a dipper circadian rhythm [17, 18]. Non-dipping of nocturnal BP seems to be a determinant of cardiac remodelling and LV diastolic dysfunction (LVDD) and may result in a cardiovascular risk independent of the increase in LVM in both hypertensive patients and in normotensives [19]. Twenty-four ambulatory blood pressure monitoring (24-ABPM) values of average systolic pressure, unlike office measurements, correlate with LVH indices in hypertensive subjects [20]. The data also suggest that early structural cardiac changes such as an increase in septal thickness and a decrease in LV ejection time are related to ambulatory blood pressure profile [21]. However, there are conflicting data regarding the relationship between the circadian rhythm of BP, especially non-dipping nocturnal BP, and LVH and left ventricular diastolic function in patients with essential hypertension.

We hypothesized that patients with the non-dipper pattern would have a more pronounced left

ventricular hypertrophy and diastolic dysfunction than patients with the dipper pattern. Accordingly, we evaluated and compared structural echocardiographic parameters in hypertensive patients known to have dipper and non-dipper characteristics during 24-h BP monitoring.

Material and methods

Study group

Data were collected from the medical records of 76 treated patients with essential hypertension who underwent ambulatory BP monitoring and transthoracic echocardiographic examination at the Department of Cardiology during a period of 14 months (from April 2009 to June 2010). Treatment was individualized and based on lifestyle and pharmacological measures. Diuretics (43%), β -blockers (34%), angiotensin-converting enzyme inhibitors (ACEI – 86%), angiotensin receptor blockers (ARB – 26%) and calcium channel blockers (38%), alone or combined, were the antihypertensive drugs most frequently used.

Hypertensive subjects can be divided into 2 groups, dippers and non-dippers, according to the presence or absence of a nocturnal fall of blood pressure of more than 10%, measured as mean arterial pressure (MAP). The MAP was defined as $MAP = 2/3 \times DBP + 1/3 \times SBP$.

Inclusion criteria were well-controlled hypertension with preserved left ventricular ejection fraction ($EF \geq 50\%$) and exclusion criteria were: severe hypertension (systolic BP (SBP) ≥ 210 mm Hg and/or diastolic BP (DBP) ≥ 115 mm Hg), secondary hypertension, significant kidney disease, valvular heart disease, heart failure and history of ischaemic heart disease. Among the patients with preserved left ventricular ejection fraction ($EF \geq 50\%$), 35 non-dippers (60 \pm 12 years, 24 males) and 26 dippers (57 \pm 13 years, 16 males) matched for age, sex, and body mass index were enrolled in this study. The control group consisted of 25 healthy individuals (53 \pm 12 years, 13 males). Echocardiographic and arterial pressure parameters were compared between dippers and non-dippers.

Ambulatory blood pressure monitoring

Ambulatory BP was recorded using an oscillometric device (Healthcare CardioNavigator V 2.601), and measurements were automatically taken every 15 min throughout 16 h during the day (07.00-23.00 h) and at 20-minute intervals during the night (23.00-7.00 h). Each ABPM dataset was first automatically scanned to remove artefactual readings, according to preselected editing criteria. Systolic readings > 260 mm Hg or < 70 mm Hg and diastolic readings > 150 mm Hg or < 40 mm Hg were automatically discarded. The recording was then ana-

lysed to obtain 24 h, day-time and night-time average SBP, DBP and heart rates.

Echocardiography

Transthoracic echocardiographic examination was performed with Vivid 7 GE with measurements of chamber dimensions taken from 2D mode, mitral inflow and calculation of LV mass and relative wall thickness (RWT). Linear measurements were made according to the European Society of Echocardiography [22]. Left ventricle volumes used to estimate ejection fraction (EF) were determined using the modified biplane Simpson's method. The protocol included assessment of mitral inflow pattern (in apical four-chamber view with the pulse Doppler sample volume at the tips of opened mitral valve leaflets). All echocardiographic measurements were performed by a cardiologist with subspecialty training in echocardiography. For LV mass the coefficient of variability for intra-observed repeated measures was less than 5%.

Relative wall thickness (RWT) was defined as [23]: $RWT = 2 \times LVPWd / LVDd$, where: LVPWd – posterior wall diastolic thickness, LVDd – left ventricular diastolic diameter. LV mass was calculated according to the Devereux formula: $LV\ mass\ (g) = 1.04 \times ((LVDd + IVSd + LVPWd)^3 - LVDd^3) - 13.6$, where: LVDd – left ventricular diastolic diameter, IVSd – intraventricular septal diameter, LVPWd – posterior wall diastolic thickness. The left ventricular mass index (LVMI) was obtained as an indicator of LVH by echocardiography as a ratio of LVM and body surface area.

LV hypertrophy (LVH) was defined by LVMI thresholds of 125 g/m² for men, and 110 g/m² for women. Left ventricular relative thickness and left ventricular mass defined left ventricular geometric patterns – normal geometry, concentric remodeling, eccentric hypertrophy and concentric hypertrophy. Concentric LV hypertrophy – $RWT \geq 0.42$ with an increased LVMI; eccentric LV hypertrophy – increased LVMI with an $RWT < 0.42$; concentric remodeling – $RWT \geq 0.42$ with a normal LVMI.

Diastolic function was assessed by recording mitral flow with standard pulsed Doppler technique, and measurements of early diastolic peak flow velocity (E), late diastolic peak flow velocity (A) and the ratio of early to late flow velocity peaks (E/A ratio).

We accepted E/A ratio < 1 as an indicator of delayed relaxation profile; E/A > 2 as typical for restriction; and values of E/A between 1 and 2 as either normal (or) pseudonormal pattern. Since the deceleration time of early waves shows a strong inverse correlation with left ventricular filling pressure, well documented with systolic dysfunction, we used the deceleration time below 150 ms as a simplified criterion of pseudonormalization. Pseudonormal pattern was also recognised with patients with a prolonged difference between duration of atrial reversal flow in the pulmonary vein and mitral flow in atrial phase, $\Delta t \geq 20\ ms$ [24, 25].

Statistical analysis

Values are expressed as means ± standard deviations (SD) or as percentages. Differences between groups were assessed by analysis of variance (ANOVA). Mean values for dipper and non-dipper patients were compared using Student's *t*-test for independent samples. χ^2 test was used to compare categorical variables between groups. Correlations were obtained by using Pearson's linear regression model. Values of *p* below 0.05 were considered statistically significant. Data management and statistical analysis were performed using Med-Calc V. 6.14. (Frank Schoonjans, Belgium).

Results

Demographic and clinical characteristics of the study population are reported in Table I with no significant differences between the studied groups.

By definition, non-dippers showed higher average systolic and diastolic pressure during the night, although 24-hour blood pressure was similar between the groups (Table II).

Table I. Clinical characteristics of study population

Parameter	Dipper (n = 26)	Non-dipper (n = 35)	Statistical significance
Age [years]	57 ±13	60 ±12	NS
Sex (M/F)	16/10	24/11	NS
BMI [kg/m ²]	27.8 ±5.4	29.6 ±4.4	NS
Normal weight/overweight/obese [%]	35/38/27	20/43/37	NS
Duration of hypertension [months]	54 (6-192)	43 (10-216)	NS
Daytime SBP [mm Hg]	123.15 ±12.9	118.04 ±11.2	NS
Daytime DBP [mm Hg]	71.3 ±9.6	67.6 ±9.1	NS

BMI – body mass index, BMI 19-24.99 kg/m² – normal weight, BMI 25-29.99 kg/m² – overweight, BMI > 30 kg/m² – obese, DBP – diastolic blood pressure, SBP – systolic blood pressure

Expectedly, in comparison with the normotensive group, patients with hypertension displayed larger ventricles and left atrium, thicker left ventricular walls and higher LV mass and mass index and lower mean EF and E/A ratio (Table III).

No statistically significant differences were found between dippers and non-dippers as regards ejection fraction, chamber dimensions, wall thickness, left ventricular mass and mass index and E/A ratio; i.e. the 2 groups did not significantly differ in left atrial diameter, end-diastolic diameter, end-systolic diameter, interventricular wall thickness, or posterior wall thickness (Table III).

According to echocardiographic measurements, 37 of the 61 patients (60.7%) were found to have LVH (left ventricular mass index LVMI > 125 g/m² in men and >110 g/m² in women). LVH was concentric in 35 patients and eccentric in the remaining 2 patients (Table IV). There was a statistically significant difference in LV geometric pattern distri-

Table II. Comparison of 24-h BP data. ANOVA test with Tukey's multiple comparison post-test was used

Parameter	Group A dippers (n = 26)	Group B non-dippers (n = 35)	Value of p
Night-time SBP [mm Hg]	103 ±13	114 ±13	< 0.001
Night-time DBP [mm Hg]	56 ±9	61 ±10	0.022
Night-time MABP [mm Hg]	72 ±10	80 ±11	0.004
24-hour SBP [mm Hg]	118 ±13	117 ±11	NS
24-hour DBP [mm Hg]	67 ±9	66 ±9	NS
24-hour MABP [mm Hg]	85 ±10	83 ±9	NS

SBP – systolic blood pressure, DBP – diastolic blood pressure, MABP – mean arterial blood pressure (MABP = 2/3 × DBP + 1/3 × SBP)

Table III. Comparison of echocardiographic data. ANOVA test with Tukey's multiple comparison post-test was used

Parameter	Group A dippers (n = 26)	Group B non-dippers (n = 35)	Group C controls (n = 25)	Value of p	Value of p A vs. B	Value of p A vs. C	Value of p B vs. C
LVd [mm]	47 ±4	49 ±4	44 ±5	0.004	NS	NS	< 0.01
LVs [mm]	32 ±4	35 ±3	33 ±5	NS	NS	NS	NS
LV PWd [mm]	11 ±2	12 ±1	11 ±1	0.016	NS	NS	< 0.05
LV PWs [mm]	15 ±2	15 ±1	13 ±1	< 0.0001	NS	< 0.01	< 0.001
LV IVSd [mm]	12 ±2	13 ±2	11 ±1	0.01	NS	NS	< 0.01
LV IVSs [mm]	15 ±2	16 ±2	12 ±2	0.0002	NS	< 0.01	< 0.001
LA [mm]	41 ±6	43 ±6	36 ±3	0.0004	NS	< 0.05	< 0.001
RV [mm]	26 ±2	27 ±3	23 ±2	< 0.0001	NS	< 0.001	< 0.001
EF [%]	59 ±5	55 ±5	62 ±3	0.0002	NS	NS	< 0.001
E/A	1.0 ±0.3	0.8 ±0.3	1.4 ±0.5	< 0.001	NS	< 0.05	< 0.001
LV mass [g]	241 ±62	291 ±67	158 ±40	< 0.001	NS	< 0.001	< 0.001
LV mass index [g/m ²]	125 ±36	142 ±31	94 ±17	< 0.001	NS	< 0.001	< 0.001
RWT (relative wall thickness)	49 ±8	50 ±6	47 ±11	NS	NS	NS	NS

LVd – left ventricular diastolic diameter, LVs – left ventricular systolic diameter, LV PWd – posterior wall diastolic thickness, LV PWs – posterior wall systolic thickness, LV IVSd – interventricular septum thickness in diastole, LV IVSs – interventricular septum thickness in systole, LA – left atrial diameter, RV – right ventricular diameter, EF – left ventricle ejection fraction, E/A – transmitral E wave velocity/transmitral A wave velocity ratio, LV mass – left ventricular mass, RWT – relative wall thickness

Table IV. Comparison of left ventricular geometric patterns between dipper and non-dipper groups (χ^2 test was used for comparison of proportions)

Group	Normal LV geometry	Concentric remodelling	Concentric hypertrophy	Eccentric hypertrophy
Dippers n = 26; 100%	3 (11.5%)	11 (42.3%)	10 (38.5%)	2 (7.6%)
Non-dippers n = 35, 100%	3 (8.6%)	7 (20%)	25 (71.4%)*	0 (0%)

*p < 0.043

bution between the two groups ($p = 0.043$). This was due to the increased prevalence of concentric hypertrophy in non-dippers compared to dippers (71.4% vs. 38.5%).

Discussion

We studied the relationship between left ventricular mass (LVM) and 24 h ambulatory blood pressure monitoring (ABPM) in 61 patients with treated, long-standing, well-controlled hypertension.

The main finding of our study is increased prevalence of concentric LVH in the night-time non-dipper group. It has also been suggested that non-dipping could be responsible for the development of left ventricular hypertrophy. This was in disagreement with other studies which have addressed this issue. In the study by Cuspidi *et al.* [26] in a selected population of 111 subjects with a recent diagnosis of hypertension no differences were found in the correlation of daytime and night-time SBP and DBP with left ventricular mass and carotid wall thickness. Also in another study published by Cuspidi *et al.* [27] no differences in cardiac structure, analysed as a continuous variable, as well as prevalence of LVH, were found in relationship to dipping or non-dipping status in the treated essential hypertensives with or without BP control. In this group the extent of nocturnal BP decrease was not associated with LV mass or LVH prevalence. Therefore, the non-dipping profile did not identify hypertensive patients with greater cardiac damage. Cuspidi *et al.* concluded that a blunted reduction in night-time blood pressure does not play a major role in the development of cardiovascular changes during the early phase of essential hypertension. The association between diurnal BP profile and target organ damage remains controversial. On the other hand, in a previous study by Cuspidi *et al.* [28] they suggested that the eccentric type of LVH, not the concentric, was the more frequent pattern in chronically treated patients. Moreover, the persistence of LVH was significantly dependent on BP levels achieved during treatment; indeed the prevalence of LVH was very low in patients with optimal BP control, whereas it was higher (37%) in uncontrolled cases. Similarly to our results, Balci *et al.* [4] found that ventricular hypertrophy was higher in the non-dipper group compared to the dipper group (42.9% vs. 6.3%, $p < 0.03$), yet it was eccentric, not concentric. In addition, the findings of Cuspidi *et al.* [29] and Stenehjem *et al.* [30] suggest that the contribution of a blunted reduction in nocturnal BP to enlarged LV mass is significant and may play a pivotal role in the development of LVH, during the early phase of essential hypertension. Moreover, subjects in whom the nocturnal decrease in blood pressure is blunted (non-dippers) have been report-

ed to have a greater prevalence of organ damage and a less favourable outcome. A blunted fall in nocturnal BP also reflects the high level of cardiovascular risk in these patients. Nevertheless, in some studies the prognostic value of this phenomenon was lost when multivariate analysis included 24-h average blood pressure [3, 11, 12]. In agreement with our results, Felicio *et al.* [31] suggest that higher nocturnal systolic BP (NSBP) levels might be responsible for an increased prevalence of LVH in hypertensive patients with type 2 diabetes. However, in another study which enrolled diabetic patients, echocardiographic structural alterations correlated more strongly with systolic BP means than with non-dipper/dipper BP ratio [32].

Cicconetti *et al.* [33] selected 23 dippers and 17 non-dippers affected by newly diagnosed, never treated hypertension, who underwent 24-h ABPM and M-mode echocardiography. They found no significant differences between these 2 groups as regards the echocardiographic left ventricular and atrial dimensions or regarding the left ventricular mass, left ventricular mass index, or relative wall thickness. We obtained similar results. In our study all echocardiographic parameters – both ventricles and left atrium, left ventricular walls, LV mass, LV mass index and E/A ratio – were similar in dippers and non-dippers. In addition, Cicconetti *et al.* found no significant differences in the rate of either left ventricular remodelling or left ventricular hypertrophy. They suggested that in the early phases of hypertension, non-dipping status was not associated with a higher level of cardiac involvement as compared to dipping status. In contrast we found significant differences in the rate of left ventricular hypertrophy between groups.

The prevalence of left ventricular hypertrophy (LVH) has been mostly documented in populations of patients with essential hypertension [34], and selected hypertensive cohorts such as children. Left ventricular hypertrophy is common in children with newly diagnosed hypertension. As systolic ABP variables increase, there is greater likelihood for increased LVMI. Although the risk for LVH is associated with increased SBP, those patients with eccentric LVH had significantly higher DBP [35]. Brady *et al.* [36] even suggested that the initial examination of these children should include echocardiography, because neither the severity of casual BP elevation nor the presence of abnormal ambulatory BP results at initial diagnosis are predictive of LVH.

It was concluded that LVH was related mainly to continuous systolic hypertension, and that LV diastolic dysfunction was related mainly to continuous diastolic hypertension. Therefore, it was suggested that LVH and LV diastolic dysfunction in hypertensive patients are caused by different mechanisms.

Nevertheless, we did not observe a significant correlation either between LVH and high systolic pressure, or between LV diastolic dysfunction and high diastolic pressure.

Grossman *et al.* [37] also reported that in 60 patients with essential hypertension LVM was poorly related to both casual and exercise blood pressure, but was related to ABPM. They considered that blood pressure load is the best determinant of LVH. After evaluation of almost 150 hypertensives, Pascual *et al.* [38] found that the principal factor related to the presence of LVH is the value of systolic blood pressure throughout a 24-h period. Feola *et al.* [39], in their study on untreated patients with essential hypertension, obtained similar results where they found that systolic ambulatory BP was significantly correlated with LVMI, while diastolic BP was not.

Numerous studies have addressed the predictive value for cardiovascular risk of the night-time BP as documented by ambulatory monitoring [40]. There are several mechanisms that could be responsible for a lower fall of BP during sleep [41]. The relationship between BMI and non-dipping was analysed. Cuspidi *et al.* [42] suggested that hypertensive patients with overweight had a reduced nocturnal BP fall and greater cardiac organ damage as compared with their lean counterparts, despite a similar overall BP load. In their study the prevalence of dipper pattern was 15% lower in the overweight group as a whole, with a 17% difference in men and 13% in women. The prevalence of left ventricular hypertrophy was higher in patients with overweight, too. Nevertheless, in the study of Chamontin *et al.* [43], the non-dipper group showed a higher diurnal and nocturnal pulse pressure and a greater left ventricular mass index, in spite of their body mass index being almost identical to that of the dipper group. In our study mean body mass index was similar between dipper and non-dipper groups (27.8 ± 5.4 vs. 27.9 ± 4.6). Despite the similar mean value, in the non-dipper group there were more patients whose BMI was above the reference values, with 37.14% obese and 42.86% overweight individuals vs. 26.92% obese and 38.46% overweight patients in the dipper group.

In our study we found that hypertensive patients compared to controls presented larger dimensions of both ventricles and left atrium, thicker left ventricular walls, and higher LV mass and mass index. These findings occurred independently of sex, age, BMI and diurnal BP levels. We also found impaired diastolic function in the hypertensive group of patients. Our data are in agreement with the study of di Bello *et al.* [44]. They compared pre-hypertensive and hypertensive patients with subjects without hypertension and found a higher LVMI in the first two groups. Moreover, they evaluated LV

diastolic function using Doppler mitral flow velocity and PW-TDI recording at the mitral annulus level. They found that in hypertensive groups mild diastolic dysfunction was associated with systolic pressure load, and cardiac remodelling.

In the present work, the non-dipper group had a greater prevalence of concentric left ventricle hypertrophy, while concentric remodelling was not significantly higher in the dipper group. We have concluded that non-dipping seems to be responsible for the increased prevalence of concentric LVH in long-standing hypertension. We have suggested that the contribution of a blunted reduction in nocturnal BP to LVH is significant. It could be possible that the conversion from non-dipping to dipping pattern during treatment may play a role in the regression of myocardial hypertrophy.

It is our opinion that ABPM should be encouraged in the diagnosis and treatment of all hypertensive subjects as it gives information about the extent of night-time decrease, which could be a possible explanation for the high prevalence of LVH.

Our study included subjects with different onset, severity, and treatment modalities of hypertension. The small number of subjects may have influenced our results, such as the absence of statistical significance concerning prevalence of LV concentric remodelling in both studied groups. All study measurements were performed on patients under anti-hypertensive medications.

Additionally, our results are based only on 2D-mode echocardiographic technique and measurements. Although accepted for clinical investigation, this method is inferior to reference 3D echocardiographic or magnetic resonance based measurements of left ventricular mass.

In conclusion, the concentric type of LVH is the prevalent pattern in non-dippers. Non-dipping blood pressure pattern may be responsible for the development of left ventricular concentric hypertrophy secondary to hypertension.

Acknowledgments

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