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Assessment of left ventricular function and peripheral vascular arterial stiffness in patients with dipper and non-dipper hypertension

Yan Chen,[1,2] Ju-Hua Liu,[1,3] Zhe Zhen,[1] Yuan Zuo,[1] Qingshan Lin,[4] Mingya Liu,[2] Chunting Zhao,[2] Min Wu,[2] Gaozhen Cao,[2] Run Wang,[2] Hung-Fat Tse,[1,2,5] Kai-Hang Yiu[1,2,5]

[1]Division of Cardiology, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China
[2]Division of Cardiology, Department of Medicine, The University of Hong Kong Shenzhen Hospital, ShenZhen, China
[3]Department of Geriatric, Affiliated Hospital of North Sichuan Medical College, Hong Kong, China
[4]Division of Radiology, Department of Medicine, The University of Hong Kong Shenzhen Hospital, Hong Kong, China
[5]Faculty of Medicine, Research Centre of Heart, Brain, Hormone and Healthy Aging, The University of Hong Kong, Hong Kong, China

Correspondence to
Dr Kai-Hang Yiu, Cardiology Division, Department of Medicine, The University of Hong Kong, Kai-Hang, China; khkyiu@hku.hk

YC and J-HL contributed equally.

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ABSTRACT

A non-dipper pattern of high blood pressure is associated with increased risk of organ damage and cardiovascular disease in patients with hypertension. The aim of the study was to evaluate the left ventricular (LV) remodeling and function and arterial stiffness in a dipper/non-dipper pattern of high blood pressure in patients with hypertension. A total of 183 hypertensive patients with no history of adverse cardiovascular events were divided into two groups based on 24 hours ambulatory blood pressure monitoring (ABPM): 66 patients with a dipper pattern and 117 patients with non-dipper pattern. Detailed transthoracic echocardiogram was performed and analyzed with advance speckle tracking 3-orthogonal direction strain analysis to assess LV systolic function and tissue Doppler-derived E/E′ for LV diastolic function assessment. Cardio ankle vascular index (CAVI) was used to evaluate arterial stiffness. Compared with patients with dipper hypertension, those with non-dipper hypertension had increased LV mass index, higher prevalence of eccentric and concentric LV hypertrophy, more impaired LV diastolic and systolic function and peripheral arterial stiffness. Multivariable analysis revealed that a non-dipper pattern was independently associated with LV systolic dysfunction evaluated by speckle tracking-derived strain analysis. In conclusion, a non-dipper pattern of hypertension is an independent risk factor for LV systolic dysfunction. Treatment that could reverse this non-dipper pattern may reduce cardiac damage in these patients.

Significance of this study

What is already known about this subject?

- A non-dipper pattern of high blood pressure is associated with increased risk of organ damage and cardiovascular disease in patients with hypertension.

What are the new findings?

- Compared with patients with dipper hypertension, those with non-dipper hypertension had increased left ventricular (LV) mass index, higher prevalence of eccentric and concentric LV hypertrophy, more impaired LV diastolic and systolic function and peripheral arterial stiffness. Importantly, a non-dipper pattern is an independent risk factor for impaired LV systolic function in patients with hypertension.

How might these results change the focus of research or clinical practice?

- All patients with uncomplicated hypertension should thus consider ambulatory blood pressure monitoring or other novel methods to document their nocturnal blood pressure pattern to better enable risk stratification and personalized treatment strategies.

INTRODUCTION

Hypertension has been reported to be associated with adverse cardiovascular events and mortality.[1] It is thus important to identify patients who are at high risk before adverse events develop. Ambulatory blood pressure monitoring (ABPM) is increasingly recommended in routine clinical practice.[2] As well as being used to evaluate variable blood pressure (BP) readings in the office or at home, it enables the detection of a non-dipping pattern of BP, a strong predictor of adverse events.[3 4] A non-dipper BP pattern is also associated with end-organ damage such as left ventricular hypertrophy,[5] although data are conflicting.[6]

Strain analysis derived by speckle tracking is a sensitive marker of subclinical myocardial dysfunction and is superior to conventional echocardiography techniques. Furthermore, the cardio ankle vascular index (CAVI) is a marker of arterial stiffening that is independent of BP and more reproducible than conventional assessment by brachial-ankle pulse wave velocity.[7] These measures of subclinical cardiovascular abnormalities have not been compared in hypertensive patients with a dipper or non-dipper pattern of BP. The aim of the present study was to determine left ventricular (LV) myocardial structural

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and functional alteration using speckle tracking-derived strain analysis and arterial stiffness evaluated with CAVI in patients with dipper and non-dipper hypertension.

METHOD

Study population

From January 2014 to April 2016, 183 consecutive patients with essential hypertension, aged over 18 years and managed at the University of Hong Kong Shenzhen Hospital were invited to participate in the study. Hypertension was defined as systolic blood pressure (SBP) >140 mm Hg and/or diastolic blood pressure (DBP) >90 mm Hg or if the subject was prescribed antihypertensive medication. Patients with previous history of cardiovascular disease including myocardial infarction, coronary artery disease, congenital heart disease, valvular disease, atrial fibrillation/flutter, heart failure, stroke or significant peripheral vascular disease were excluded. Patients with poor quality echocardiography images, secondary hypertension, thyroid function disorder and chronic renal or liver disease were also excluded. This study was part of the Chinese Hypertensive Heart Study aim to evaluate cardiovascular manifestations, pattern of disease, pathophysiology and therapies in Chinese patients with hypertension. The study was approved by the ethics committee of the University of Hong Kong Shenzhen Hospital according to Declaration of Helsinki. All participants gave written informed consent.

Clinical and laboratory examinations

All patients received a complete physical examination and a clinical assessment to establish baseline characteristics. Blood samples were collected in all study participants after overnight fasting to measure glycated hemoglobin (HbA1c), lipid profile and serum creatinine. Current smoking status, body mass index (BMI; kg/m^2) and patient's history of diabetes mellitus (DM) and hyperlipidemia were documented. The use of drugs such as calcium channel blocker (CCB), beta-blocker, ACE inhibitor (ACEI) or angiotensin receptor blocker (ARB) and diuretics was also recorded.

24 hours ambulatory blood pressure monitoring

A portable non-invasive recording device, the Meditech ABPM-05, was used to record 24 hours ambulatory BP values at 30 min intervals. Patients continued their normal daily routine and were recorded the times at which they slept and awakened. All data were loaded into ABPM report management system software and finally analyzed using the ABPM-FIT program. For each 24 hours measurement, overall, night-time and daytime mean SBP and DBP values were recorded, and mean artery pressure (MAP) for daytime and night-time was calculated by the formula: DBP+(SBP−DBP)/3. Non-dipper hypertension was defined as a night-time MAP decrease of <10% from the daytime MAP.[3] The percentage decline in night-time MAP was calculated as follows: 100×(1–night-time MAP/daytime MAP). If the night-time MAP declined by ≥10%, patients were classified as 'dippers', and if they declined by <10%, they were classified as 'non-dippers'.

Arterial stiffness assessment

Through an oscillometric method, CAVI integrates the cardiovascular elasticity derived from the aorta to the ankle pulse velocity. It is an accurate assessment of vascular stiffness and does not depend on BP.[8] In this study, CAVI was automatically measured and calculated at rest using a VaSera VS-1000 device (Fukuda Denshi, Tokyo, Japan). An average of the right and left CAVI value was used to assess arterial stiffness.

Conventional and speckle tracking echocardiography

All patients were imaged in left lateral decubitus position at rest using an echocardiography system (Vingmed E9, General Electric Vingmed Ultrasound, Milwaukee, Wisconsin, USA). A 3.5-MHz transducer was used to collect images and subsequently stored in cine-loop format. Offline analysis was performed using EchoPAC V.112.0 (General Electric—Vingmed, Horten, Norway). The interventricular septum thickness, posterior wall thickness and LV dimension were measured in M-mode at end-diastole from the parasternal long-axis view according to the current recommendations.[9] LV volume and ejection fraction were obtained using Simpson's method. LV mass was calculated using ASE formula[9] and indexed to body surface area. LV hypertrophy (LVH) was defined as increased LV mass index (LVMI) (≥96 g/m^2 in females; ≥116 g/m^2 in males). Normal LVMI was defined as <96 g/m^2 in females and <116 g/m^2 in males.[9] Relative wall thickness (RWT) was calculated using the ASE formula: RWT=2× posterior wall thickness/left ventricular dimension in diastole, and increased RWT was defined as RWT >0.42, and normal RWT was defined as RWT ≤0.42.[9] LV structural pattern was defined as: normal (normal LVMI and normal RWT); concentric remodeling (normal LVMI and increased RWT); eccentric hypertrophy (LVH and normal RWT) or concentric hypertrophy (LVH and increased RWT). LV based on the pulsed-wave Doppler of mitral valve inflow, measuring peak early diastolic velocity (E), peak late (A) diastolic velocity and calculating E/A ratio, diastolic function was assessed. Pulsed-wave tissue Doppler imaging was used to measure the early diastolic velocity (E′) at the septal and lateral annulus, then mean E′ was calculated. In addition, E/E′ ratio was evaluated to estimate LV filling pressure.[10] Two-dimensional (2D) speckle tracking strain analysis that can provide detailed assessment of myocardial deformation was used to assess myocardial systolic function. LV global longitudinal strain (LS), circumferential strain (CS) and radial strain (RS) were respectively assessed from three orthogonal directions. LS is expressed as negative value and determined by the average value of 18 LV segments from three apical views. CS is also expressed as negative value and derived by the average value of six LV segments from short axis view. RS was also obtained from the average value of six LV segments in short axis view but expressed as a positive value.

STATISTICAL ANALYSIS

Data are expressed as mean±SD for continuous variables. Frequencies or proportions for presenting categorical variables. Normal distribution of variables was assessed by Kolmogorov-Smirnov test. Comparison between patients with dipper and non-dipper hypertension were analyzed by independent Student's t-test (all normal distribution parameters) or Mann-Whitney U test (non-normal distribution parameters including hypertension duration, HbA1c and triglyceride) for continuous

Table 1 Clinical data for dipper and non-dipper hypertensive patients

Variables	Total (n=183)	Dipper (n=66)	Non-dipper (n=117)	p Value
Demographic data				
Age, years	46.5±12.6	44.6±11.3	47.5±13.2	0.131
Male, n (%)	106 (57.9)	42 (63.6)	64 (54.7)	0.240
Body mass index, kg/m^2	26.1±4.1	25.6±3.9	26.4±4.2	0.174
Body surface area, m^2	1.79±0.21	1.79±0.19	1.79±0.23	0.862
Medical history				
Hypertension duration, years	5.0±5.7	4.1±4.9	5.3±5.8	0.201
Diabetes mellitus, n (%)	22 (12.0)	7 (10.6)	15 (12.8)	0.658
Hyperlipidemia, n (%)	63 (34.4)	25 (37.9)	38 (32.5)	0.460
Current smoker, n (%)	31 (16.9)	13 (19.7)	18 (15.4)	0.455
Medication				
ACEI/ARB, n (%)	67 (36.6)	17 (25.8)	50 (42.7)	0.022
CCB, n (%)	138 (75.4)	51 (77.3)	87 (74.4)	0.660
Beta-blocker, n (%)	42 (23.0)	10 (15.2)	32 (27.4)	0.060
Diuretic, n (%)	30 (16.4)	14 (21.2)	16 (13.7)	0.186
Clinical data				
Office SBP, mm Hg	152.7±25.6	154.4±29.4	151.8±23.3	0.520
Office DBP, mm Hg	93.5±17.6	95.6±19.6	92.3±16.4	0.226
Daytime SBP, mm Hg	138.5±15.2	139.8±15.1	137.8±15.3	0.381
Daytime DBP, mm Hg	87.2±12.9	89.2±12.9	86.1±12.8	0.117
Night-time SBP, mm Hg	129.3±14.9	121.8±12.2	133.5±14.7	<0.001
Night-time DBP, mm Hg	80.9±12.0	76.7±11.1	83.1±11.9	<0.001
24 hours mean SBP, mm Hg	134.3±14.1	131.2±13.1	136.1±14.3	0.026
24 hours mean DBP, mm Hg	84.6±12.0	83.4±11.9	85.2±12.0	0.349
Daytime MAP, mm Hg	104.3±12.7	106.1±12.5	103.3±12.7	0.154
Night-time MAP, mm Hg	97.0±11.9	91.7±10.5	99.9±11.7	<0.001
24 hours mean heart rate, bpm	75.0±9.7	75.1±11.0	75.0±8.9	0.890
Blood chemistry				
HbA1c, %	5.8±1.0	5.8±1.0	5.7±1.0	0.699
TG, mmol/L	1.7±0.9	1.7±0.9	1.8±0.9	0.507
TC, mmol/L	4.7±1.1	4.7±1.1	4.8±1.1	0.667
HDL, mmol/L	1.2±0.3	1.2±0.3	1.2±0.4	0.759
LDL, mmol/L	3.1±0.9	3.1±1.0	3.0±0.9	0.605
Creatinine, mmol/L	74.1±19.7	76.4±20.4	72.8±19.2	0.278

Except where otherwise indicated, values are the mean±SD or n (%).
ACEI, ACE converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAP, mean artery pressure; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

variables, and X^2 test for categorical variables. In order to determine an independent association of non-dipper BP pattern with LV myocardial strains, E/E´ and CAVI, multivariable linear regression analysis adjusting for age, gender, cardiovascular risk factors and medication was performed for the whole study population. All statistical analyses were calculated using the statistical package SPSS for windows (V.21.0, SPSS, Chicago, Illinois, USA). All tests were two-sided for consistency and $p<0.05$ was considered to be statistically significant.

RESULTS

Clinical characteristics

The mean age of the study population was 46.5±12.6 years and 57.9% were male. Among the total population, 66 (36.1%) patients were determined to be dippers, and 117 (63.9%) were non-dippers. The clinical characteristics for patients with dipper and non-dipper hypertension are shown in table 1. Compared with dippers, patients with a non-dipper pattern had higher night-time SBP, DBP and MAP, and higher 24 hours mean SBP, as well as a higher percentage of ACEI/ARB use. No significant differences were noted between patients with the dippers and non-dippers for the remaining demographic, clinical or laboratory parameters.

Echocardiographic parameters and arterial stiffness

The echocardiography parameters and arterial stiffness are shown in table 2. The LV posterior wall thickness, RWT and LVMI were significantly larger in patients with non-dipper hypertension. The type of LV geometry differed between patients with dipper and non-dipper hypertension; patients with non-dipper hypertension had a higher prevalence of eccentric and concentric LVH. Furthermore, patients with non-dipper hypertension had a higher ratio of E/E′, indicating more impaired LV diastolic function. Importantly, global LV systolic strains derived by 2D speckle tracking in all three orthogonal directions were more impaired in

Table 2 Comparison of LV function and arterial stiffness between dipper and non-dipper hypertensive patients

Variables	Total (n=183)	Dipper (n=66)	Non-dipper (n=117)	p Value
IVSD, cm	1.05±0.16	1.03±0.16	1.06±0.16	0.149
LVDD, cm	4.74±0.52	4.73±0.52	4.75±0.52	0.775
LVPWD, cm	1.00±0.15	0.96±0.12	1.01±0.16	0.018
RWT	0.42±0.07	0.41±0.06	0.43±0.07	0.034
LVMI, g/m^2	98.1±26.8	92.3±22.3	101.3±28.6	0.029
LV geometry				
Normal, n (%)	63 (34.4)	32 (48.5)	31 (26.5)	0.001
Concentric remodeling, n (%)	57 (31.1)	23 (34.8)	34 (29.1)	
Eccentric LVH, n (%)	32 (17.5)	6 (9.1)	26 (22.2)	
Concentric LVH, n (%)	31 (16.9)	5 (7.6)	26 (22.2)	
LVEDV, mL	83.4±22.7	81.2±20.9	84.6±23.6	0.332
LVESV, mL	30.9±11.6	29.8±11.8	31.5±11.4	0.328
LVEF, %	63.8±5.2	64.4±5.0	63.4±5.3	0.180
E/A ratio	1.00±0.29	1.03±0.28	0.99±0.30	0.357
E/E′ ratio	8.24±2.28	7.62±2.03	8.58±2.35	0.006
LS, %	−18.7±3.1	−19.6±3.1	−18.2±3.0	0.003
CS, %	−18.6±3.5	−19.9±3.5	−17.8±3.3	<0.001
RS, %	32.4±9.3	36.6±10.0	29.8±7.9	<0.001
CAVI, m/s	8.12±1.32	7.83±1.08	8.29±1.43	0.025

Except where otherwise indicated, values are the mean±SD or n (%).
A, peak velocity of mitral inflow in early diastole; CAVI, cardio ankle vascular index; CS, circumferential strain; E, peak velocity of mitral inflow in late diastole; E/A ratio, ratio of peak velocity of mitral inflow in early and late diastole; E/E′, ratio of early diastolic mitral velocity to mean peak early diastolic velocity at septal and lateral annulus; E′, mean peak early diastolic velocity at septal and lateral annulus; IVSD, interventricular septum thickness at end-diastole; LS, longitudinal strain; LV, left ventricular; LVDD, left ventricular dimension at end-diastole; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; LVH, LV hypertrophy; LVMI, LV mass index; LVPWD, LV posterior wall thickness at end-diastole; RS, radial strain; RWT, relative wall thickness.

non-dippers than dippers. With reference to peripheral vascular parameter, patients with non-dipper hypertension had a higher CAVI, indicating more severe arterial stiffness.

The relationship between non-dipper hypertension and cardiovascular abnormalities

The relationship between a dipper/non-dipper pattern of hypertension and cardiovascular abnormalities in patients with hypertension is described in table 3. Univariate analyses showed that non-dipper hypertension was significantly associated with LS (B=1.39, 95% CI 0.49 to 2.29, p=0.003), CS (B=2.08, 95% CI 1.02 to 3.14, p<0.001), RS (B=−6.77, 95% CI −9.52 to −4.02, p<0.001), E/E′ (B=0.96, 95% CI 0.28 to 1.64, p=0.006) and CAVI (B=0.46, 95% CI 0.06 to 0.86, p=0.025). Multivariable linear regression analysis adjusting for age, gender, cardiovascular risk factors and medication demonstrated that a non-dipper pattern remained independently associated with LS, CS and RS (all p<0.05). Nonetheless, no such relationship was noted between non-dipper BP pattern and E/E′ or CAVI after multivariable adjustment analysis (table 3).

DISCUSSION

The present study demonstrated that a non-dipper pattern in hypertensive patients without prior cardiovascular complications is associated with increased LVMI, a higher prevalence of eccentric and concentric LVH, impaired LV diastolic and systolic function and increased arterial stiffness compared with a dipper pattern. Importantly, a non-dipper pattern is an independent risk factor for impaired LV systolic function in patients with hypertension.

BP fluctuates every minute and shows a circadian rhythm over 24 hours with a normal fall >10% in the night. A non-dipper pattern of hypertension, which is defined as lack of nocturnal BP decline with fall <10% that of the daytime BP, has been shown to be associated with a higher risk of cardiovascular and cerebrovascular diseases.[11–13] Studies have demonstrated that among patients with hypertension, non-dippers have a higher incidence of LVH and reduced LV diastolic function compared with dippers,[14 15] although results are conflicting.[6] With a larger study sample, our study demonstrated that patients with non-dipper hypertension had increased LVMI, a higher prevalence of eccentric and concentric LVH and more impaired diastolic function presenting as increased E/E′ ratio than those with dipper hypertension. Although this finding can be partially explained by elevated BP, non-dipper status played a key role that can directly activate components of the renin-angiotensin-aldosterone system and consequently be responsible for LV remodeling and diastolic dysfunction.[16] Furthermore, a non-dipper pattern of hypertension promotes arterial stiffening, independent of daytime BP[17] and can promote additional LV remodeling and subsequent diastolic dysfunction.[18]

For the assessment of LV systolic function in patients with hypertension, a previous study evaluating LV dyssynchrony

Table 3 Evaluation of the independent association of non-dipper hypertension with cardiovascular abnormalities

	Myocardial involvement								Atrial stiffness	
	LS		CS		RS		E/E′-mean		CAVI	
Variables	B (95% CI)	p Value	B (95% CI)	p Value	B (95% CI)	p Value	B (95% CI)	p Value	B (95% CI)	p Value
Non-dipper/dipper hypertension										
Unadjusted	1.39 (0.49 to 2.29)	0.003	2.08 (1.02 to 3.14)	<0.001	−6.77 (−9.52 to −4.02)	<0.001	0.96 (0.28 to 1.64)	0.006	0.46 (0.06 to 0.86)	0.025
*Adjusted	1.04 (0.12 to 1.96)	0.028	1.90 (0.73 to 3.07)	0.002	−6.52 (−9.51 to −3.53)	<0.001	0.55 (−0.07 to 1.16)	0.079	0.24 (−0.12 to 0.60)	0.196

*Adjusted for age, gender, body mass index, 24 hours mean SBP and DBP, hypertension duration, diabetes mellitus, hyperlipidemia, current smoker, ARB or ACEI, CCB, beta-blocker, diuretics, resistant hypertension.
B, unstandardized regression coefficient; CAVI, cardio ankle vascular index; CS, circumferential strain; E/E′, ratio of early diastolic mitral velocity to mean peak early diastolic velocity at septal and lateral annulus; LS, longitudinal strain; RS, radial strain.

using tissue Doppler imaging has demonstrated that patients with non-dipper hypertension have a higher frequency of LV contraction dyssynchrony compared with dippers.[19] Another cross-sectional study that assessed ventricular systolic function using isovolumic acceleration has shown that patients with non-dipper hypertension have increased biventricular subclinical systolic dysfunction compared with those with dipper hypertension.[20] Furthermore, Gokdeniz *et al* found that LV rotational mechanics are impaired in non-dippers compared with dippers in hypertensive patients with type 2 DM.[21] These studies were nonetheless limited by their small sample size and technique limitations such as angle dependency of tissue Doppler imaging, and high observer variability for analysis of rotational parameters. The present study used speckle tracking-derived myocardial strain analysis, a proven accurate and sensitive method for the evaluation of subclinical myocardial dysfunction,[22] and confirms that patients with non-dipper hypertension had impaired strain in three orthogonal directions compared with those with dipper hypertension. This may be due to the increased LVMI and higher prevalence of eccentric and concentric LVH that may affect myocardial deformation in patients with non-dipper hypertension. Another possible explanation is that the non-dipper pattern is characterized by persistent hypertension that extends to the nocturnal period; the continuous high BP may accumulate cardiac wall stress and further contribute to the development of myocardial contraction dysfunction. The observed impaired myocardial function thus provides further evidence of the increased cardiovascular risk of non-dipper pattern in hypertensive patients. Treatment that could reverse a non-dipper BP pattern, for example, taking medication in the night, may potentially reduce LV remodeling and myocardial dysfunction in patients with hypertension.[23]

Arterial stiffness is one of the earliest features of adverse structural and functional changes within the arterial wall, often assessed by CAVI, and is recognized as a marker of cardiovascular disease.[24] A recent study has revealed significantly increased CAVI in adolescent hypertensive patients compared with controls.[25] Another previous report showed that patients with non-dipper hypertension had increased carotid intima media thickness compared with those with dipper hypertension.[26] The present study confirms that patients with non-dipper hypertension had a higher CAVI value than dippers. This association can be explained by an increased inflammatory response[27] that is closely related to arterial stiffness.[28] The significant correlation between non-dipper pattern and arterial stiffness assessed by CAVI was nonetheless neutralized after multivariable adjustment and only age and DM were independent predictors of arterial stiffness in patients with hypertension. These findings suggest that factors such as age and DM may contribute more than a non-dipper pattern to the increased arterial stiffness. The exact mechanism of increased arterial stiffness in patients with a non-dipper pattern of hypertension thus requires further evaluation.

CLINICAL IMPLICATIONS

A non-dipper pattern of hypertension is associated with target organ damage and poor long-term outcome. The present study provides firm evidence that a non-dipper pattern is associated with adverse LV remodeling, diastolic dysfunction and impaired myocardial strain in otherwise uncomplicated hypertensive patients. This observation further supports the assessment of dipper/non-dipper pattern by ABPM in all patients with hypertension and may help identify those with subclinical myocardial damage before the development of adverse outcomes. All patients with uncomplicated hypertension should thus consider ABPM or other novel methods to document their nocturnal BP pattern to better enable risk stratification and personalized treatment strategies.

LIMITATIONS

A major limitation of the current study is cross-sectional design in which there was a lack of prognostic data in terms of future cardiovascular events. Second, diagnosis of dipper and non-dipper hypertension was based on a single 24 hours ABPM. Finally, three-dimensional echocardiography was not performed to evaluate cardiac function, particularly in assessing right ventricular and atrial function.

CONCLUSIONS

This study demonstrates that a non-dipper pattern of BP in patients with hypertension was associated with a higher prevalence of subclinical adverse LV remodeling, impaired LV function and greater arterial stiffness. Identifying a dipper/non-dipper pattern of BP in uncomplicated patients with hypertension improves risk stratification and may prevent premature adverse events.

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