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REVIEW

Clinical Conditions and Predictive Markers of Non-Dipper Profile in Hypertensive Patients

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Hypertension remains one of the primary causes of premature cardiovascular mortality representing a major independent risk factor.
The importance of ambulatory blood pressure monitoring in clinical evaluation of hypertensive patients, beyond diagnosis, is the identification of circadian dipping/non-dipping profile. The non-dipper pattern in hypertensive and normotensive patients is associated with significant target organ damage and worse outcomes, as an increased cardiovascular risk condition. Non-dipping pattern has been found to be associated with specific clinical conditions. Obesity, diabetes mellitus, metabolic syndrome, obstructive sleep apnea syndrome, chronic kidney disease, autonomic and baroreflex dysfunctions, salt sensitivity, hormonal changes, gender and age were extensively studied. Research efforts are focused on recognizing and exploring predictive markers of abnormal blood pressure circadian pattern. Previous studies acknowledge that red cell distribution width, mean platelet volume, fibrinogen level, C-reactive protein, serum uric acid and gamma-glutamyltransferase, are independently significant and positive associated to non-dipping pattern. Moreover, research on new biomarkers are conducted: Chitinase 3-Like-Protein 1, atrial and B-type natriuretic peptide, brain-derived neurotrophic factor, chemerin, sphingomyelin and the G972R polymorphism of the insulin receptor substrate-1 gene. This review summarizes the current knowledge of different clinical conditions and biomarkers associated with the non-dipper profile in hypertensive patients.

Keywords: systemic hypertension, non-dipper profile, cardiovascular risk, clinical conditions, predictive markers

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Introduction

Hypertension was identified as a main preventable cause of morbidity and premature mortality worldwide, 31.1% adults suffering from this condition. Hypertension prevalence displays a significant difference between high-income and low-and middle-income countries. [1]

Different approaches to treatment, awareness and control along with additional increase of life expectancy, grant the emerging incidence of hypertension. [2]

In 2012 hypertension prevalence in Romanian population was 40.4% as reported by SEPHAR II survey. 85% patients were taking antihypertensive treatment and adequate control was obtained in a quarter. [3]

SEPHAR III survey (2016) results revealed an ascending prevalence, with 19.1% newly diagnosed hypertensive patients out of 45.1% total prevalence. [4]

Ambulatory blood pressure monitoring (ABPM) is the recommended standard method in accurate diagnosis of true high blood pressure (BP), systolic and diastolic values along with all particular aspects of the circadian BP variation. [5,6]

The dipper profile is defined by at least 10% decline, but not more than 20% in systolic and/or diastolic BP value during the night-time, compared to daytime. The term non-dipper refers to patients whose blood pressure does not exhibit these variations. [6] Non-dipper hypertensive patients manifest an increased mortality risk, cardiac and extracardiac morbidity. [7,8]

Possible underlying mechanisms of non-dipper profile were explored in a multitude of studies conducted over the years, identifying clinical conditions linked to disturbances of 24-h systolic and/or diastolic BP variations. [9]

Complex mechanisms originating in endocrine, renal, neural, and vascular areas are involved in the pathogenesis of arterial hypertension and its circadian variability. Poor sleep quality and the absence of physical exercise during the day, are likely affecting the abnormal night-to-day BP ratio. (Table I)

Significant target organ damage (TOD) such as left ventricular hypertrophy, stroke, changes in carotid wall thickness and atherosclerotic plaques, along with renal and ocular damage were recognized in non-dipper hypertensive patients. [7,8,21,22]

Non-dipper profile is not a static marker of the cardiovascular status. Hypertension pattern identification and therapeutic interventions can improve patient prognosis. [23-25]

This review summarizes the current knowledge of different clinical conditions and biomarkers associated with the non-dipper profile in hypertensive patients.

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Table I. Conditions associated with non-dipping pattern

Endocrine system disorders	Hypo/Hyperthyroidism [9,10] Primary hyperparathyroidism [11] Aldosteronism [9] Cushing syndrome [9] Pheochromocytoma [10] Hypopituitarism [12] Impaired nocturnal melatonin secretion [13] Acromegaly [14]
Renal dysfunction	Chronic kidney disease [10] Renal transplantation [15] Unilateral nephrectomy [16]
Autonomic nervous system dysfunction	Autonomic failure Orthostatic hypotension [17, 18]
Sleep disturbances	Obstructive sleep apnea [10] Stress disorders [19] Impaired sleep quality [20]
Other [10]	Obesity Diabetes mellitus Metabolic syndrome Salt sensitivity Age, gender

Autonomic nervous system

Neural mechanisms are believed to play an important role in non-dipper hypertension profile.

Increased autonomic nervous system activity is involved in triggering and maintaining high BP. Different techniques were used to measure sympathetic nervous system (SNS) activity: electrophysiological studies and measurement of norepinephrine neurotransmitter values in plasma and urine samples. [26]

Dauphinot and colab. report that patients with impaired autonomic nervous system activity present an insufficient decrease in nocturnal BP. [27] Non-dipper hypertensive patients have low circulating norepinephrine and higher peripheral vascular resistance compared to dippers. [28]. Grassi et al. provide evidence that in arterial hypertension is a close correlation between the sympathetic activation degree and the magnitude of nocturnal decrease in systolic or diastolic BP. [10,29]

Orthostatic hypotension

Orthostatic hypotension is a relatively common and multifactorial disorder, often secondary to autonomic dysfunction. BP variation related to posture was associated to non-dipper pattern in female gender taking at least 2 antihypertensive drugs. Orthostatic hypotension could be a marker of non-dipper profile. [30]

Alquadan et al. demonstrated that postprandial hypotension and cardiac rhythm variability computed on ABPM are potent predictors of autonomic dysfunction in routine clinical practice. [31] Frequently, patients with orthostatic hypotension may develop non-dipper hypertension profile, which is a treatment challenge for physicians. [18]

Obesity

Compared to normal weight, obesity is responsible for five times increase in hypertension incidence. [32] In the complex obesity-associated hypertension process, activation of renin-angiotensin-aldosterone system (RAAS), endothelial and adipose tissue dysfunction and the sympathetic nervous system (SNS) stimulation, represents the underlying mechanisms. [33-35]

Through pathological activation of RAAS, in visceral adipocytes renin-angiotensin-aldosterone metabolites involved in BP regulation are released: angiotensinogen, renin and renin receptor, angiotensin-converting enzyme, angiotensin I type and angiotensin II receptors. Angiotensinogen via angiotensin II induce hypertension by systemic vasoconstriction, sodium and fluid balance, and stimulates aldosterone secretion. [33]

The role of metabolic dysregulation in obesity-associated hypertension implies the malfunction of connection between microvascular and perivascular adipose tissue inflammation to adipokine and neuropeptides synthesis. Leptin, resistin, adiponectin, visfatin, TNF- α, IL-6, MCP-1 and IL-1 further disturb the sympathetic activity and influence the tight link with insulin resistance. Both mechanisms are responsible in hypertension development. [33,36,37]

Different studies observed that basic mechanisms of obesity-associated hypertension are very much alike to mechanisms determinants of non-dipping pattern of hypertension. [10,38-40]

Ayukusuma et al. in a small study investigated the serum level of interleukin-6 (IL-6), as a key mediator of mechanism between hypertension and inflammation. Performed on forty-eight hypertensive patients, study concluded that IL-6 serum level did not differ among dipper and non-dipper hypertensive patients. [41]

Diabetes mellitus and metabolic syndrome

Decline of physiological mechanisms in hypertensive patients with diabetes mellitus or metabolic syndrome (MS), are considered to be also responsible for the non-dipper hypertension pattern: insulin resistance (anti-diuretic action of insulin), exaggerated response to internal vasoconstrictors, surge of SNS activity, damage endothelium-vasodilatation dependant and results of thickening in vascular smooth muscle. [10]

Duggal and colab. showed that 46% of hypertensive patients with type 2 diabetes had a non-dipper profile. This profile is associated to higher prevalence of microalbuminuria and advanced age. Authors emphasize the importance of BP profile identification and early specific treatment in particular patients, stratified as patients at increased risk of cardiovascular and renal mortality and morbidity. [42]

BP pattern of hypertensive patients taking antihypertensive medication and presenting metabolic syndrome, were also studied by Tartan et al. using the MS-Score. A predictive role of high MS-Score for the non-dipping pattern of BP was proved. [43]

In addition, abdominal obesity associated with increased level of uric acid in patients with MS was closely related to non-dipper blood pressure profile as it was suggested by Tutal et colab. [44]

Metabolic syndrome pathophysiology that underlies the increase of arterial stiffness in non-dipper patients, determine aortic function damage, through exposer of the aortic wall to additional pressure load. Non-dipper obese hypertensive patients had an enlarged thoracic aortic diameter compared to dipper patients. [45]

Karaagac et al. demonstrated that for non-dipper hypertensive patients associating MS, specific 12-lead electrocardiogram parameters are valuable for assessing the increased cardiovascular morbidity and mortality risk. The interval between the peak (Tp) and the end (Te) of T wave, Tp-Te interval, is an index of total dispersion of myocardial repolarization. Combined with Tp-Te/QT ratio (QT- extension of the time between the beginning of the Q wave, and the intersecting descending part of T wave to isoelectric line) and Tp-Te/QTc ratio (QTc- corrected QT) these markers of potential ventricular arrhythmias were significantly higher and very strong associated to the non-dippers with metabolic syndrome. [46]

Obstructive sleep apnea

Obstructive sleep apnea (OSA) syndrome severity directly influence the non-dipping pattern. Despite mild severity of OSA, transient hypoxemia and hypercapnia caused by recurrent episodes of apnea, trigger changes in SNS activity and disrupt night sleep. [10] An increased OSA severity reduces the dipping pattern, augmenting the non-dipper number of OSA patients. [47]

Normotensive and hypertensive OSA patients are more affected by impaired nocturnal BP decrease than regular normotensive or hypertensive patients. [48] Apnea-hypopnea index has a significant association to non-dipper profile and no association to age or body mass index. [49]

Wolf et al. summarized the potential pathways of causative relation of OSA to non-dipper pattern: endothelium damage, oxidative stress, high levels of plasma asymmetric dimethyl arginine concentration and elevated L-selectin, ICAM-1 (intercellular adhesion molecule-1) and VCAM-1(vascular cell adhesion molecule-1). [50]

In obese patients with MS and OSA syndrome treatment with continuous positive airways pressure, upper airway surgery or stimulation, can improve BP circadian variations and reduces cardiovascular risk. [47,51]

Hormones

Routledge et al. analysed 47 menopausal women ABPM recordings. Non-dipper female patients (34%) were older and had lower stress scores compared to dipper participants. [52]

Research in perimenopausal hypertensive women reported 61.5% non-dipper profile in a sample of 130 participating women. Non-dipper profile in perimenopausal women more often associates obesity, postural hypotension, microalbuminuria, and elevated glycosylated haemoglobin, fibrinogen, C-reactive protein. [53]

Thyroid

Systolic and diastolic BP were investigated in relation to serum thyrotropin (TSH), in patients presenting elevated TSH levels with typical disease manifestation or subclinical form of hypothyroidism. Within normal TSH limits, a positive association was found between both, systolic (>160 mm Hg) and diastolic (>95 mm Hg) hypertension, and TSH serum. [54]

Nevertheless, a recent study presented results supporting the theory that hypertensive patients with subclinical hypothyroidism more frequently experience a diastolic non-dipper profile. [55]

Possible pathway of determining the non-dipper pattern in hypothyroidism is the result of increase vascular resistance under SNS influence. [10]

Concerning other thyroid hormones, an independent association of non-dipping pattern to low level of free triiodothyronine was reported in a study by Kanbay et al. investigating patients with no thyroid hormone disorder. [56]

Parathyroid hormone

Kanbay et colab. reported that non–dipper pattern in hypertensive patients is significantly associated to higher levels of phosphate, Calcium x Phosphorus product, and parathyroid hormone level. [57]

Chronic kidney disease

Prospective and cross-sectional studies in chronic kidney disease (CKD) patients have demonstrated changes in 24-h BP pattern that may support kidney function worsening. Mechanisms involved include RAAS provocation, endothelin activation, inflammation, altered baroreceptor sensitivity and SNS activity. [58]

CKD patients have a higher prevalence of non-dipping pattern and elevated mean systolic overnight BP, results shown by monitoring 1805 patients in Ancona Hypertension Centre, Italy. [59] Aggregate data confirm that personalised therapy (selection of drugs, dosage and chronotherapy) is needed in order to prevent long-term cardiovascular events and TOD in abnormal BP variations of CKD hypertensive patients. [58,59]

Non-dipper pattern is a negative determinant in the nephropathy evolution in type 1diabetes patients and a risk factor for microalbuminuria evolution. [60]

In renal transplantation patients, assessing the Doppler renal resistive index proved to be a strong predictor for non-dipper profile. [61] Presence of abnormal circadian BP variation at one year in kidney transplantation patients, increases the risk of transplanted kidney failure in the next 3-4 years. [62]

Non-dippers with reduced left ventricular ejection fraction (LVEF) have increased incidence of renal and cardiovascular worse outcomes, compared to dippers. In non-diabetic patients affected by decreased glomerular filtration

rate and progression of renal disease, 24-h ABPM and LVEF can be used as prognostic markers. [63]

Extended research is also conducted for identification of potential pathways of salt-induced non-dipper profile in hypertensive patients.

Data derived from a study conducted on 115 young never treated hypertensives patients, suggested that G972R insulin receptor substrate-1 gene (IRS-1) polymorphism, is associated with insulin resistance, salt sensitivity and non-dipper hypertension. [64] Heterozygous carriers exposed to high salt diet develop non-dipper hypertensive profile.

Decrease in night-time BP was identified in groups of salt sensitive hypertensive patients with sodium intake restriction. [65]

Elevated concentrations of plasma norepinephrine, CKD with attenuated inhibition of RAAS, impaired renal sodium excretion and genetic factors were recognized as responsible for salt-induced non-dipper hypertensive profiles. [66]

Therapeutic strategy

Current guidelines on treatment and management of hypertension do not recommend personalised treatment in dipper and non-dipper hypertensive patients. [6]

However, the 2016 European Guideline on cardiovascular disease prevention in clinical practice, indicates the assessment of dipping pattern or suspicion of non-dipping in CKD or diabetes mellitus patients or OSA patients. [67]

Table II. Current laboratory predictive biomarkers of non-dipper hypertension profile

Author, year	Participant number	Biomarker	Results in non-dipper subjects	Study conclusion
Tosu, 2014. [74]	120	Uric acid	Significantly higher levels compared to dippers/control group (p < 0.05)	In non-dippers, increased inflammatory markers can be the reason of advanced end-organ failure in conjunction with cardiovascular morbidity and mortality.
		C-reactive protein		
		Red blood cell distribution width (RDW)	Significantly higher than dippers/normotensives (p<0.05)	
Buyukkaya, 2016. [75]	170	RDW	Higher values compared to dippers 14.5 ± 0.87 vs.12.7 ± 0.66, p<0.001	High values of commonly hematological element (RDW) may be linked to inflammatory state, in normotensive and hypertensive non-dipper patients.
		hs-CRP	Higher hs-CRP levels 0.99 ± 0.52 vs.0.63 ± 0.43, p<0.001	
Kaya, 2010. [76]	126	Mean platelet volume (MPV)	Higher levels compared to normotensives and dippers 9.72+/-0.52fl vs 8.92+/-0.42fl and 9.38+/-0.33fl, p<0.05	Inflammatory activity and raised platelet activation pattern are present in non-dipper hypertensive patients, increasing the atherosclerotic risk.
		hs-CRP	Significantly raised compared to normotensives and dippers 4.9+/-1.7mg/l vs 2.7+/-0.8mg/l and 3.8+/-1.5mg/l, p<0.05	
Ortakoyluoglu, 2016. [77]	171	Gamma-glutamyl-transferase (GGT)	Significant increased versus dipper 36.2±13.8 vs 20.5±8.8 U/L, p=0.03	GGT positively associated to non-dipper profile; negatively related to night-to-day BP variation.
Tabara, 2016. [78]	1020	BNP plasma	Positively related to circadian BP variations (p<0.001)	Mild elevation of BNP plasma level identified as marker of atypical BP circadian variation along with abnormal pattern of nocturnal BP.
		Oxygen desaturation (SpO2)	Positive association OR:1.04, p=0.001	
Bakirci, 2015. [79]	80	YKL-40 levels	Significantly greater compared to dippers 183.1 ± 59.1 versus 125.9 ± 50.3 pg/mL, p<0.001	Higher level of YKL-40 serum, hs-CRP together with epicardial adipose tissue thickness were independently markers of non-dipper pattern; it can constitute an improved prediction tool for prevention and immediately treatment of high risk non-dipper induced cardiovascular outcome.
Ji, 2017. [80]	60	CD4+ effector T (Teff) cells: Th1, Th2, Th17	Th1 and Th17 notably higher compared to the dippers Th2 level significantly higher in dippers when compared to non-dippers	Th1 and Th17 subsets response were independently associated with the non-dipper pattern. TOD, hypertension prevention and treatment could benefit out of adjusting the CD4+ effector T cells.
Kadoya, 2014. [81]	250	Plasma BDNF	Intermediate value compared to highest value determined in reverse-dippers	Connection between autonomic nervous system activity, evaluated through BDNF plasma level, with abnormal BP circadian pattern.
Meric, 2014. [82]	90	Chemerin (tazarotene-induced gene 2 protein-TIG2)	Higher levels 219.7±16.3 vs. 182.4±21.4 ng/ml -dipper; p<0.001 219.7±16.3 vs. 85.4±38.1 ng/ml-normotensive; p<0.001	By determining the chemerin level in non-dipper hypertensives, clinical decision can be improved in high risk hypertensive patients. Results reinforced the inflammation role in pathophysiology of high BP.
Zheng, 2014. [83]	116	Sphingomyelin	Significance of systolic and diastolic BP night decline was negatively correlated to plasma SM level; r=-0.42, p<0.01 for systolic BP and r=-0.31, p<0.01 for diastolic BP	SM levels assessment may be applied in detection of high risk cardiovascular patients, linked to non-dipper pattern.
Cayli, 2013. [84]	317	Serum hs-cTnT	Absolute predictor for non-dipper pattern OR:1.409; 95% CI, 1.276–1.556; p<0.001	Serum hs-cTnT and NT-proBNP value demonstrate autonomous prediction for non-dipper profile in hypertensive patients; serum hs-cTnT values are related to night time systolic BP. Newly diagnosed hypertensive patients, can benefit from the potency of high sensitivity cardiac troponin T marker.
		NT-proBNP	Independent marker of non-dipper pattern; OR:1.012; 95% CI, 1.005–1.020; p=0.001	

Nevertheless, treatment strategies based on dipper/non-dipper status is an emerging novel concept for high-risk hypertensive patients. Recent studies contribute with close supporting evidence for personalized treatment approach in the non-dipper BP pattern. [68]

For the non-dippers, initiation or treatment adjustment along with choronotherapy, would determine highest benefit of antihypertensive therapy. Reducing the number of the non-dipping hypertensive patients will ensure long-term protection over cardiovascular events in patients presenting TOD, insulin resistance and increased proteinuria and fibrinogen levels. [69]

Bedtime administration of novel calcium channel blockers (barnidipine, cilnidipine) prove to restore normal dipping profile in most of OSA /non-OSA hypertensive patients. [24,25]

Kario et al. showed that administration of an alpha-adrenergic blocker (doxazosin) at bedtime reduced blood pressure overnight in non-dipper pattern. [70]

In a systematic review conducted by Wang on 3732 patients, chronotherapy could invert non-dipper profile in hypertensive CKD subjects with no significant disparities for cardiovascular and all-cause mortality. [71]

In CKD hypertensive patients, bedtime valsartan administration in non-dippers provided renal protection by slowly decreasing the glomerular filtration rate and low 24 hours proteinuria. A better protection of the target organs was computed. [72] Diuretic therapy or salt restriction in CKD patients, restore the dipper pattern by normalising sodium excretion. [73]

Research efforts are focused on the detection of dipper/non-dipper profile predictive markers. (Table II)

Conclusions

At present, available data support the evidence of certain clinical conditions related to non-dipper pattern.

Confirming the circadian BP variation with specific night-to-day BP ratio, is appropriate to investigate possible secondary causes of high BP, medication adjustment (dosage and chronotherapy) along with therapeutic drug and response monitoring. Antihypertensive therapeutic approach dependent on dipper/non-dipper profile represents an innovative, advanced concept aimed to maximize treatment response in high risk hypertensive patients.

Further studies are needed to reinforce the clear position of circadian blood pressure profile in practical aspects of hypertension.

Conflict of interest

None to declare.

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