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The relationship between white coat hypertension and the index of cardiac electrophysiological balance (ICEB)

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ABSTRACT

Aim: The index of cardiac electrophysiological balance (ICEB) is a new marker that can show the potential for ventricular arrhythmia and indicate the balancebetween ventricular depolarization and repolarization. A tendency toward ventricular arrhythmia has been shown innon-dipper hypertension and prehypertensive patients in various studies. White coat hypertension (WCH) has been shown to be associated with target organ damage and the actual development of hypertension. In this study, we aimed to evaluate the effect of dipper and non-dipper patterns on the ICEB in patients diagnosed with WCH.

Material and Method: A total of 108 patients were included in this study. Patients were divided into two groups as dipper and non-dipper patterns according to ABPM. QT/QRS (ICEB) and cQT/QRS (ICEBc) were recorded with computerized interpretation of the electrocardiogram.

Results: While electrocardiographic parameters including heart rate, PR interval, QT interval, cQT interval, and ICEB were similar in both groups (p>.05), in the non-dipper group, QRS duration was lower (p=.017) and ICEBc was higher (p=.001).

Conclusion: ICEBc may predict asusceptibility to ventricular arrhythmias in WCH patients. Therefore, non-dipper WCH patients with a high ICEBc should be followed for arrhythmia outcomes in addition to hypertensive outcomes.

Keywords: White coat hypertension, non-dipper pattern, the index of cardiac electrophysiological balance, electrocardiography, ventricular arrhythmia, QT interval

INTRODUCTION

White coat hypertension (WCH) is a condition in which home blood pressure (BP) or ambulatory BP measurements (ABPM) are normal, but outpatient measurements are high (1). Although it appears to be a benign condition, it has been shown to be associated with target organ damage and the actual development of hypertension (2,3). Normal blood pressure shows a circadian rhythm. At night, blood pressure decreases by more than 10% compared to the average daytime value; this is called a dipping pattern. A non-dipping pattern is a reduction in blood pressure of less than 10% at night and is associated with increased cardiovascular risk and target organ damage (1,4,5). Supraventricular and ventricular arrhythmias are causes of cardiovascular morbidity and mortality. Predicting these dysrhythmias and initiating early treatment or avoiding the causative conditions can reduce morbidity and mortality. Many studies have shown a predisposition to ventricular arrhythmias in patients with non-dipper hypertension and left ventricular hypertrophy (6–8). A tendency toward ventricular arrhythmia in patients with prehypertensive non-dipping pattern is demonstrated by a fragmented QRS (9). The predictive value of the frontal QRS axis, which demonstrate myocardial repolarization, has been demonstrated in patients with non-dipper hypertensionand without left ventricular hypertrophy (10). In the evaluation of arrhythmia, electrocardiographic (ECG) findings such as QT dispersion, QTc, Tp-e (Tp-e=peak-to-end interval of the T wave), Tp-e/QT have been evaluated in many studies (11–14). The index of cardiac electrophysiological balance (ICEB) is the ratio of QT to QRS (QT/QRS), which is a new marker that can show the potential for ventricular arrhythmia and is easily calculated on asurface ECG (15). It has been demonstrated that ICEB can be used in place of cardiac wavelengthλ (λ= effective refractory period [ERP] x conduction velocity [CV]), which is measured in anelectrophysiology laboratory and can

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indicate the balance between ventricular depolarization and repolarization (16). An imbalance may predispose one to Torsades de Pointes (TdP) and other ventricular arrhythmias. In this study,we aimed to evaluate the effect of dipper and non-dipper patterns on ICEB in patients diagnosed with WCH.

MATERIAL AND METHOD

This retrospective study was carried out with the permission of Ankara Keçiören Training and Research Hospital, Non-Invasive Clinical Researches Ethics Committee (Date: 09.11.2021, Decision No: 2012-KAEK-15/2424). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection

In our study, patients with a systolic blood pressure (SBP) of ≥140 mmHg and/or a diastolic blood pressure (DBP) of ≥90 mmHg in a physical examination and who underwent ABPM with suspected WCH (the blood pressure readings in the hospital were higher than they are in other settings, such as the home) were evaluated from May 2020 to July 2021. In accordance with the 2018 European Society of Cardiology (ESC) / European Society of Hypertension (ESH) guidelines (1), 151 patients were diagnosed with WCH. A detailed physical examination was performed on the patients and medical history was taken. Demographic and laboratory data were obtained from the automated hospital system and recorded. Diagnoses of hypertension on ABPM records, diabetes mellitus, chronic kidney disease, coronary artery disease, left ventricular systolic dysfunction (EF<50%) and moderate-severe valve disease in echocardiography, endocrine diseases (hyperthyroidism, anemia), obstructive sleep apnea syndrome, chronic obstructive pulmonary disease, pregnancy, drug use affecting the autonomic nervous system, branch block, atrial fibrillation, and atrioventricular block on an ECG were determined as exclusion criteria. Forty-three patients with one or more of the exclusion criteria were excluded from the study.

ABPM Recordings

Twenty-four-hour ambulatory blood pressure recordings were obtained using the oscillometric system (Altgasse 68 6341 Baar, Switzerland). Daytime recordings were made between 06:00 and 22:00, nighttime recordings were madebetween 22:00 and 06:00. Blood pressure values were taken every 30 minutes for daytime recordings and were taken every hour at nighttime. Information about sleep duration was obtained from the patients, and no adverse events related to the device were reported during the day or at night. It was required that the false measurement rate be less than 20%. Daytime, nighttime, and 24-hour systolic, diastolic, and mean blood pressures were obtained from ABMP recordings. A 24-hour mean of ≥130/80 mmHg, daytime mean of ≥135/85 mmHg, and nighttime mean of≥120/70 mmHg were accepted as hypertension, and clinical blood pressure measurements were SBP ≥140 mmHg and/or DBP ≥90 mmHg; those with normal ABPM values were considered WCH (1). A dipper pattern was determined as a ≥10% decrease in mean blood pressure during the nighttime, according to the mean blood pressure value during the daytime, and a ≥10% decrease in mean blood pressure was a non-dipper pattern (1). The patients diagnosed with WCH were divided into two groups, dipper and non-dipper, according to ABPM records.

Electrocardiography and Echocardiography

A 12-lead surface ECG was obtained from all patients, in the supine position, after resting for at least 5 minutes. Heart rate, PR, QRS, QT, and cQT intervals were obtained from computerized interpretation of the electrocardiogram results (Nihon Kohden, Tokyo, Japan). Also, QT/QRS(ICEB) and corrected QT (QTc)/QRS (ICEBc) values were calculated from these ECG data for every patient. Transthoracic echocardiography was performed on all patients with GE Healthcare Vivid S60N. Left ventricular diastolic diameter, interventricular septum, and posterior wall measurements were taken on the parasternal long axis just below the mitral valve tips in diastole to calculate the left ventricular mass and index (17). The left ventricular ejection fraction was measured by using the modified Simpson's method (17). Left ventricular hypertrophy was evaluated according to the LV (left ventricle) mass index. LV mass was calculated with the following formula: Lv mass=0,8x(1,04x((LVEDD (left ventricle end diastolic diameter)+IVSd (Interventricular septum distance)+PWd (posterior Wall distance))3-LVEDD3)))+0,6. LV mass index was calculated using the following formula: LV mass index=LV mass/Body surface area (BSA) (17). BSA was calculated with the Mosteller Formula: BSA= ([height(cm)x weight(kg)]/3600)1/2. Values >95 g/m^2 for women and >115 g/m^2 for men were accepted as left ventricular hypertrophy.

Statistical Analysis

Numerical data were expressed as mean standard deviation, and non-numeric data as a percentage (%). Data were saved in the SPSS version 23.0 statistics program. Continuous variables with normal distribution were compared with the Student t-test. The Pearson method was used in the correlation analysis of the independent variables in each population studied.

RESULTS

The mean age of the entire population in our study was 52.8, and 52% of the dipper group and 50% of the non-dipper group were women. There was no difference between the two groups in terms of body-mass index and smoking, respectively (p=.426,p=.882). Transthoracic echocardiographic parameters, left ventricular ejection fraction (LVEF), left ventricle end-diastolic diameter (LVEDD), interventricular septum thickness (IVST), and posterior wall thickness (PWT) were examined, and no significant difference was observed in both groups (p>.05). In addition, there was no statistically significant difference between the two groups in terms of left ventricular hypertrophy (p>.05) (**Table 1**). There was no difference between the two groups in terms of hemoglobin and electrolyte values (p>.05). While forthe ABPM records, the 24-h mean SBP was not statistically different between the two groups (p>.05), the 24-h mean DBP was significantly higher in the dipper group (p<.001). Daytime SBP and DBP were significantly higher in the dipper group (p=.024 ,p<.001), and nighttime SBP was significantly higher in the non-dipper group (p=.002)(**Table 2**). While electrocardiographic parameters including heart rate, PR interval, QT interval, cQT interval, and ICEB were similar in both groups (p>.05), in the non-dipper group, QRS duration was lower (p=.017) and ICEBc was higher (p=.001) (**Table 3**).

Tablo 1. Demographic laboratory and echocardiographic features

Variable	Dippers (n=50)	Non-dippers (n=58)	P value
Age, years	51.06±9.7	52.97±9.5	0.310
Gender			
Male, n (%)	24 (48%)	29 (50%)	0.838
Female, n (%)	26 (52%)	29 (50%)	
Body-mass index, kg/m^2	28.15±3.7	28.74±3.9	0.426
Smoking, n (%)	26 (52%)	31 (53.4%)	0.882
LVEF, %	60.64±2.8	59.8±2.7	0.132
LV mass (g)	146.06±51.2	155.53±25.1	0.216
LV mass index (g/m^2)	74.28±9.6	81.46±11.6	0.001
LVEDD (cm)	4.68±0.36	4.68±0.29	0.976
IVST (cm)	0.87±0.06	1.08±1.06	0.172
PWT (cm)	1.03±1.00	0.96±0.08	0.604
Hemoglobin (g/dl)	14.1±1.26	16.16±1.51	0.339
Na (mEq/L)	140.1±2.3	139.1±2.8	0.114
K+ (mEq/L)	4.10±0.26	4.19±0.42	0.199
Ca (mEq/L)	9.54±057	9.52±0.44	0.980

LVEF:left ventricular ejection fraction. LV:left venricul. SBP:systolic blood pressure. DBP:diastolic blood pressure ,LVEDD:left ventricle end-diastolicdiameter IVST:interventricular septum thicknessPWT:posterior wall thickness. P value in bold :statistical significanse

Tablo 2. ABPM records

Variable	Dippers (n=50)	Non-dippers (n=58)	P value
24 h mean SBP, mmHg	118.34±8.9	116.72±8.7	0.345
24 h mean DBP, mmHg	72.38±5.58	67.26±5.77	<0.001
Daytime SBP, mmHg	122.88±9.44	119.02±8.07	0.024
Daytime DBP, mmHg	76.4±5.98	70.34±5.76	<0.001
Night-time SBP, mmHg	107.36±8.56	112.16±7.46	0.002
Night-time DBP, mmHg	63.28±5.09	63.59±5.44	0.765

SBP: systolic blood pressures DBP: diastolic blood pressures. P value in bold :statistical significanse

Tablo 3. Electrocardiographic findings

Variable	Dippers (n=50)	Non-dippers (n=58)	P value
Heart rate, beats/min	81.02±14.15	83.6±16.49	0.379
PR interval, msec	146.5±14.51	152.8±19.4	0.061
QRS duration, msec	85.30±7.82	81.38±8.84	0.017
QT interval, msec	369.80±34.99	369.31±37.75	0.945
QTc interval, msec	405.5±22.24	410.76±19.71	0.196
ICEB	4.38±0.52	4.55±0.58	0.119
ICEBc	4.78±0.45	5.09±0.64	0.001

ICEB: index of cardiac electrophysiological balance, ICEBc: index of cardiac electrophysiological balance with heart rate correction. P value in bold :statistical significanse

DISCUSSION

Hypertension is one of the most common diseases in clinical practice (1). Identifying conditions predisposing individuals to hypertension, taking the necessary precautions, and treating them contribute to areduction of morbidity and mortality (1). In addition, predicting arrhythmias that may be associated with hypertension and taking the necessary precautions may have a positive effect on outcomes in cardiovascular system-related conditions. Although WCH seems to be benign, Mancia et al. (18) showed that hypertension developed in 42.6% of WCH patients in a 10-year follow-up. In another study, it was shown that the development of hypertension was approximately three times more common compared to people with normal blood pressure (19). Not only hypertension, but also WCH has been found to be associated with cardiovascular diseases. Therefore, WCH is a relevant clinical condition. Recent studies have shown that left ventricular hypertrophy and carotid atherosclerosis are more common as target organ damage in patients with WCH than in normotensive patients (20,21). In addition, it has been shown that cardiovascular mortality is higher in patients with WCH than in normotensive or prehypertensive patients (22).

A Non-dipping pattern is a reduction in blood pressure of less than 10% at nightcompared to the average daytime value and is associated with increased cardiovascular risk and target organ damage (1,4,5). In many studies, it has been shown that the non-dipper pattern predisposes for VA (ventricular tachicardia and/or ventricula fibrillation) in patients with hypertension (6–14). Therefore, WCH may be a predisposing factor for cardiovascular diseases as well as for arrhythmia. By identifying the WCH population with a predisposition to ventricular arrhythmia, it may be possible to ensure that the agents to be selectedas antihypertensives in the future have antiarrhythmic properties or to avoid proarrhythmic agents in different treatment options. LVH has been shown to have a proarrhythmic effect in hypertensive and prehypertensive patients in studies (6–8,10). In our study population, there was no statistically significant difference between the groups in terms of LVH. LVH had no effect on our study population in terms of both ECG findings and arrhythmia. Therefore, the importance of the ICEB value as a proarrhythmic indicator was increased in our study group.

ICEB is a relatively new marker that indicatesventricular arrhythmogenesis and is obtained by dividing QT/QRS in ECG (15). Lu et al. (16) suggested that a significant increase in ICEB may cause TdP-induced VA, while a decrease may cause non-TdP-induced VA. ICEBc is the QTc/QRS ratio, and in healthy chronic smokers it may predicta tendency toward TdP-induced VA (23). It has also been shown that ICEB can predict cannabinoid-induced VA (24). In our study, ICEB values were higher in the non-dipper group, and ICEBc was found to be significantly higher. The shorter QRS duration on the depolarization side and the longer QTc interval in the direction of repolarization may explain the higher ICEBc values in the non-dipper group. It is known that non-dipper status increases the frequency of left ventricular hypertrophy and causes cardiac conduction problemsandautonomic dysfunctionand heterogeneity in ventricular repolarization (25,26). Sympathetic activity has been shown to increase in WCH patients compared to normatensives, and, in another study, anincrease in sympathetic activity and decrease in vagal activity have been shown to prolong QTc (27,28). In addition, an increase in nocturnal sympathetic activity and a decrease in vagal activity were shown in patients with the non-dipper pattern (29,30). The non-dipper state and increased adrenergic effect may cause deterioration in ventricular homogeneity, and this may be related to the ICEBc results in our study. Ultimately, non-dipper statusmay lead to increased susceptibility to ventricular arrhythmia in WCH patients.

The main limitations of our study were the small number of patients and its retrospective nature. ABPM could not be used in normotensive patients due to theretrospective nature of the study. Prospective follow-up periods were not performed for the evaluation of arrhythmia in the patients.

CONCLUSION

ICEBc was found to be significantly higher in patients with WCH and non-dipper patterns compared to those with dipper patterns. ICEBc may predict asusceptibility to ventricular arrhythmias in WCH patients. Therefore, non-dipper WCH patients with a high ICEBc should be followed for arrhythmia outcomes besides hypertensive outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Keçiören Training and Research Hospital, Non-Invasive Clinical Researches Ethics Committee (Date: 09.11.2021, Decision No: 2012-KAEK-15/2424).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

REFERENCES

1. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESHguidelines for themanagement of arterial hypertension. Eur Heart J 2018; 39: 3021-104.
2. BenDov IZ, Kark JD, Mekler J, Shaked E, Bursztyn M. The white coat phenomenon is benign in referred treated patients: a 14 year ambulatory blood pressure mortality study. J Hypertens 2008; 26: 699-705.
3. Pierdomenico SD, Lapenna D, Di Mascio R, Cuccurullo F. Short and long-term risk of cardiovascular events in white coat hypertension. J Hum Hypertens 2008; 22: 408-14.
4. Ohkubo T, Hozawa A, Yamaguchi J, et al. Prognostic significance of the nocturnal decline in blood pressure in individuals with andwithout high 24-h blood pressure: the Ohasama study J Hypertens 2002; 20: 2183–9.
5. Fukuda M, Munemura M, Usami T, et al. Nocturnal blood pressure iselevated with natriuresis and proteinuria as renal function deteriorates in nephropathy. Kidney Int 2004; 65: 621–5
6. McLenachan JM, Henderson E, Morris KI, Dargie HJ. Ventricular arrhythmias in patients with hypertensive left ventricular hypertrophy. N Engl J Med 1987; 317: 787–92.
7. Pringle SD, Dunn FG, Macfarlane PW, McKillop JH. Significance of ventricular arrhythmias in systemic hypertension withleft ventricular hypertrophy. Am J Cardiol 1992; 69: 913–7.
8. Siegel D, Cheitlin MD, Black DM, Seel. Risk of ventricular arrhythmias in hypertensive men with left ventricular hypertrophy. Am J Cardiol 1990; 65: 742–7.

9. Eyuboglu M, Akdeniz B. Association between non-dipping and fragmented QRS complexes in prehypertensive patients. Arq Bras Cardiol 2019; 112: 59-64.
10. Tanriverdi Z, Unal B, Eyuboglu M, et al. The importance of frontal QRS-T angle forpredicting non-dipper status in hypertensive patients without left ventricular hypertrophy. Clin Exp Hypertens 2018; 40: 318-23.
11. Panikkath R, Reinier K, Uy-Evanado A, et al. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increasedrisk of sudden cardiac death. Circ Arrhythm Electrophysiol 2011; 4: 441–7.
12. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death dueto cardiac arrest. Circulation 1991; 83: 1888–94.
13. Gupta P, Patel C, Patel H, et al. T(p-e)/QTratio as an index of arrhythmogenesis. J Electrocardiol 2008; 41: 567–74.
14. Akboga MK, Gulcihan Balci K, Yilmaz S, et al. Tp-e interval and Tp-e/QTc ratio as novel surrogate markers for prediction of ventricular arrhythmic events in hypertrophic cardiomyopathy. Anatol J Cardiol 2017;18: 48–53
15. Robyns T, Lu HR, Gallacher DJ, et al. Evaluation of index of cardio-electrophysiological balance (iCEB) as a new biomarker for the identification of patients at increased arrhythmic risk. Ann Noninvasive Electrocardiol 2016; 21: 294–304.
16. Lu HR, Yan GX, Gallacher DJ, et al. A new biomarker–index of cardiac electrophysiologicalbalance (iCEB)–plays an important role in drug-induced cardiac arrhythmias: beyond QT-prolongation and Torsades de Pointes (TdPs). J Pharmacol Toxicol Methods 2013; 68: 250–9
17. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiography 2015; 28: 1-39.
18. Mancia G, Bombelli M, Facchetti R, et al. Long-term risk of sustained hypertension in white-coat or masked hypertension. Hypertension 2009; 54: 226-32.
19. Sivén SSE, Niiranen TJ, Kantola IM, et al. White-coat and masked hypertension as risk factors for progression to sustained hypertension: the Finn-home study. J Hypertens 2016; 34: 54–60.
20. Fukuhara M, Arima H, Ninomiya T, et al. White-coatand masked hypertension are associated with carotidatherosclerosis in a general population: the Hisayama study. Stroke 2013; 44: 1512-7
21. Cuspidi C, Sala C, Tadic M, et al. Is white-coat hypertension a risk factor for carotid atherosclerosis? A review and meta-analysis. Blood Press Monit 2015; 20: 57–63.
22. Gustavsen PH, Høegholm A, Bang LE, et al. White coat hypertension is a cardiovascular risk factor: a 10-yearfollow-up study. J Hum Hypertens 2003; 17: 811–7
23. Özdemir L, Sökmen E. Effect of habitual cigarette smoking on the index of cardiac electrophysiological balance in apparently healthy individuals J Electrocardiol 2020; 59: 41-4.
24. Efe SC, Oz A, Guven S, et al. Evaluation of index of cardiac-electrophysiological balance as arrhythmia predictor in bonsai users. Minerva Cardioangiol 2020; 68: 559-66.
25. An HR, Park S, Yoo TH, et al. Non-dipper status and left ventricular hypertrophy as predictors of incident chronic kidney disease. J Korean Med Sci 2011; 26: 1185–90.
26. Myredal A, Friberg P, Johansson M. Elevated myocardial repolarization lability and arterial baroreflex dysfunction in healthy individuals with nondipping blood pressure pattern. Am J Hypertens 2010; 23: 255–9.
27. Grassi G, Seravalle G, Trevano FQ, et al. Neurogenic abnormalities in masked hypertension. Hypertension 2007; 50: 537–542.
28. Abildskov JA. Adrenergic effects of the QT interval of the electrocardiogram. Am Heart J 1976; 92: 210–6.
29. Kohara K, Nishida W, Maguchi M, Hiwada K. Autonomic nervous function in non-dipper essential hypertensive subjects. Evaluation by power spectral analysis of heart rate variability. Hypertension 1995; 26: 808–14.
30. Ino-Oka E, Yumita S, Sekino H, et al. The effects of physical activity and autonomic nerve tone on the daily fluctuation of blood pressure. Clin Exp Hypertens 2004; 26: 129–36.