Relationship Between Ambulatory Blood Pressure Variability and Atherogenic Index of Plasma

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Abstract

Objectives: In ambulatory blood pressure monitoring trials, non-dipper hypertensive patients had a worse cardiovascular outcome than dipper hypertension (HT) patients. However, no trials have been performed to inquire into the relationship between ambulatory blood pressure variability and coronary artery disease. In large-scale research, the atherogenic index of plasma has been found as a marker of coronary artery disease. This study inquired if there was a correlation between blood pressure variability and the atherogenic index of plasma.

Materials and Methods: The study involved 158 hypertensive patients. Patients were distributed as non-dipper HT and dipper HT according to 24-hour ambulatory blood pressure follow-up. The dipper HT group consisted of 49 individuals, while the non-dipper HT group consisted of 109 patients. Biochemistry, hemogram and echocardiographic were examined.

Results: Gender, previous diagnosis of HT, serum creatinine, hemoglobin and cholesterol, triglyceride levels were similar in both groups. The dipper HT group had more patients with diabetes (36.7% vs 13.8% p<0.001). The median age of the participants was statistically significantly higher in the non-dipper HT group [44 (22) vs. 50.5 (17.3) p=0.022]. High inflammatory markers were similar in both groups, but the atherogenic index of plasma in the dipper HT group was significantly higher than the non-dipper HT group (0.250±0.262 vs 0.141±0.262 p=0.017). In the echocardiographic comparison, the ejection fraction, relative wall thickness and left atrial diameters were similar in both groups, whereas the non-dipper HT group had a considerably larger ascending aortic diameter.

Abstract

Conclusion: The atherogenic index of plasma, which is an important predictor of coronary artery disease, was found to be higher in the dipper HT group. This is the first study to inquire into the correlation between the atherogenic index of plasma and ambulatory blood pressure change.

Keywords: Ambulatory blood pressure variability, atherogenic index of plasma, coronary artery disease

Introduction

Ambulatory blood pressure (ABP) monitoring is a method used in daily practice, giving information about the daily activities of hypertensive individuals and the blood pressure values during sleep[1,2]. It also provides important information about the prognosis of hypertensive individuals and is recommended in patient follow-up[2]. In studies on ABP variability, it was shown that blood pressure showed circadian rhythm and decreased by 10% during sleep. Individuals who show this decline are classified as "dipper" and individuals who cannot show it as "non-dipper"[2].

Coronary artery disease (CAD) is still the primary cause of death worldwide and is affected by many risk factors such as diabetes mellitus (DM), smoking, dyslipidaemia, hypertension (HT), male gender and age[3-6]. There was an increase in cardiovascular mortality in non-dipper HT individuals[1,2]. However, there is no study investigating the relationship between ABP variability and CAD.

The logarithm of the ratio of triglyceride (TG) to high-density cholesterol (HDL) is used to estimate the atherogenic index of plasma (AIP), which has been shown to be an accurate indicator of CAD[7,8]. This research aimed to see if there was an association between ABP variability and CAD using AIP, a CAD biomarker.

Materials and Methods

Study Population

The ABP monitoring of 358 patients between September 2016 and September 2018 in the Department of Cardiology of Ankara Gülhane Training and Research Hospital was reviewed. Among the patients who were admitted to the cardiology clinic with the complaint of high blood pressure and were decided to have ABP monitoring, those without known CAD were included in the study. Individuals with missing information and normotensive are excluded from the study, 158 patients without CAD were included in the study. As a criterion for inclusion in the study, it was taken as hypertensive individuals over 18 years of age who were not known to have CAD, who did not use antihypertensive and antihyperlipidemic medication or did not have blood pressure control despite using drugs. Exclusion criteria were secondary HT, renal failure, known CAD, DM with known micro and macrovascular complications. The Gülhane School of Medicine Ethics Committee of the University of Health Sciences Turkey approved the study protocol (decision no: 18/217, date: 25.09.2018).

Ambulatory Blood Pressure Monitoring

Twenty-four-hour ABP monitoring was performed using BR-102 plus (Schiller, Switzerland) devices and analysed with the appropriate software. Daytime was defined as the time interval between 08:00 a.m. and 10:00 p.m., while night-time was defined as the time interval between 10:00 p.m. and 08:00 a.m. Daytime measures were taken every 30 min, and night-time measurements were taken every 60 min. Patients were advised to continue their daily routine and medication and were told that they should be inactive during the measurement.

Results of ABP monitoring were evaluated according to 2018 European Society of Cardiology hypertension guideline recommendations[2]. The diagnostic threshold for HT is ≥130/80 mmHg over 24 h, average ≥135/85

mmHg during the day, and average ≥120/70 mmHg during the night (all comparable to office BP of ≥140/90 mmHg)[2]. Patients are recognized as 'dippers' if their nocturnal blood pressure falls by more than 10% of the daytime average blood pressure value, while less falls was accepted as non-dipper HT[2,9].

Biochemical and Echocardiographic Examinations

In the patients who participated in the trial, morning fasting blood was taken for routine biochemistry, lipid profile and hemogram tests. All the patients who participated in the study were screened with transthoracic echocardiography (Vivid 7, Wipro GE Health Care, GE Medical Systems Inc., Chicago, USA). The echocardiographic evaluation was performed according to the American Society of Echocardiography's recommendations[10]. Echocardiographic measurements were performed at the end of expiration with patients in the standard left lateral decubitus position. Interventricular septum and posterior wall thickness, as well as ascending aorta measurements, were taken at the end-diastolic phase. The modified biplane Simpson technique was used to determine the left ventricular ejection fraction (LVEF). In the parasternal long-axis view, the aortic diameter was measured. The formula 2xposterior wall thickness/end-diastolic diameter was used to compute relative wall thickness[10].

Statistical Analysis

The SPSS program was used to perform all statistical analyses (version 20.0 for Windows, SPSS Inc. Chicago, IL). The data were compared in terms of the groups and evaluated by a normal distribution of the Shapiro-Wilk test and QQ plots. Continuous variables with normal distribution were represented as mean ± standard deviation, not normal distribution was given median and interquartile range (IQR) and categorical variables were given as percentages. The Student's t-test was used to analyze continuous variables with a normal distribution. To compare numerical variables between the two groups, the paired sample t-test and Mann-Whitney U test were used. To compare categorical variables between the two groups, the chi-square test was performed. Multiple logistic regression analysis was used to analyze statistically significant outcomes in univariate analysis. A p-value of <0.05 was considered statistically significant.

Results

The study involved 158 hypertensive patients. The dipper HT group consisted of 49 individuals, while the non-dipper HT group consisted of 109 patients. Although both groups had similar clinical characteristics in terms of female gender and previous HT diagnosis, the dipper HT group had more diabetes patients (36.7% vs. 13.8% p<0.001). The median age of the participants was statistically significantly higher in the non-dipper HT group [44 (22) vs. 50.5 (17.3), p=0.022] (Table 1). In both the dipper HT and non-dipper HT groups, the mean 24-hour blood pressure was similar. Daytime systolic and diastolic blood pressure averages were considerably higher in the dipper HT group, while nighttime systolic and diastolic blood pressure mean values were significantly higher in the non-dipper HT group (Table 1). Of the patients participating in the study, 70 (44.32%) had a previous diagnosis of HT. Forty-eight (68.6%) of those with the previously diagnosed HT were in the non-dipper HT group, and 22 (31.4%) were in the dipper HT group. Forty-five (64.28%) patients with HT were taking monotherapy (100% ACE inh/ARB). Of the 45 patients who received monotherapy, 18 were in the dipper HT group and 27 were in the non-dipper HT group. Twenty-five patients (35.72%) were on dual combination therapy. Of the patients who were taking combination therapy, 18 (72%) were taking ACE inh/ARB blocker-calcium channel blocker combination, and 7 (28%) were taking ACE inh/ARB blocker-diuretic combination.

In routine laboratory examination, serum creatinine, hemoglobin, TG, low-density cholesterol, total cholesterol, HDL, red cell distribution width (RDW), levels were found to be similar in both groups (Table 2). The dipper-HT group had considerably higher AIP than

the non-dipper HT group (0.250±0.262 vs. 0.141±0.262, p=0,017) (Table 2).

In the echocardiographic evaluation, both groups had similar LV ejection fraction, left atrial diameter, and relative wall thickness, but the ascending aortic diameter was considerably greater in the non-dipper HT group (Table 3).

Multiple logistic regression analysis was used to evaluate statistically significant outcomes in univariate analysis. As a result, any variables did not accomplish statistical significance (Table 4).

Discussion

In this study, the relationship between ABP variability and AIP that is a marker of CAD was investigated and the AIP was found significantly higher in dipper HT individuals. In the previous studies, inflammatory markers

such as RDW and MPV, which were found to be higher in non-dipper HT, were similar in the dipper and non-dipper HT group[11,12]. In contrast to our initial hypothesis and expectations in our study, the AIP level was found to be higher in the dipper HT group.

ABP monitoring gives more information on mean blood pressure, blood pressure variability and diurnal variations in HT according to office and home measurements[13,14]. Many studies have also revealed that it is more directly associated with target organ damage[13,14]. The current European Society of Cardiology Hypertension Guideline recommends ABP monitoring for HT diagnosis and therapy[2].

In normal and hypertensive individuals, blood pressure tends to fall during sleep. Hypertensive individuals whose blood pressure falls less than 10% during sleep are classified as non-dipper, whereas individuals with

Table 1. Basal demographic and blood pressure characteristics

	Dipper hypertension (n=49)	Non-dipper hypertension (n=109)	p-value
Age, (years) (IQR)	44 (22)	50.5 (17.3)	**0.022**
Women, (n)	17 (34.7%)	45 (41.3%)	0.433
Diabetes Mellitus, (n)	18 (36.7%)	15 (13.8%)	**0.001**
Diagnose of previous hypertension, (n)	21 (42.6%)	49 (44.9%)	0.312
24-h Ambulatory SBP, mmHg			
Mean ± SD Median (IQR)	138.16±16.00 136.00 (20.5)	137.03±16.99 133.00 (20.50)	0.475
24-h Ambulatory DBP, mmHg			
Mean ± SD Median (IQR)	84.53±9.60 84.00 (11.50)	84.33±12.09 82.00 (14.00)	0.423
Daytime SBP, mmHg			
Mean ± SD Median (IQR)	143.16±15.10 141.00(23.50)	137.80±17.20 133.00 (17.50)	**0.015**
Daytime DBP, mmHg			
Mean ± SD Median (IQR)	89.20±9.47 88.00 (11.00)	85.66±12.65 83.00 (13.50)	**0.004**
Night-time SBP, mmHg			
Mean ± SD Median (IQR)	119.67±21.20 123.00 (19.50)	135.55±17.99 131.00 (21.50)	**<0.001**
Night-time DBP, mmHg			
Mean ± SD Median (IQR)	72.02±9.71 71.00 (12.50)	81.66±11.90 79.00 (16.00)	**<0.001**

Significant p-values are shown in bold.
SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SD: Standard deviation, IQR: Interquartile range, n: Number

10% or more are classified as dipper hypertensive[1,2,9]. Non-dipper HT is associated with sleep disturbances, obstructive sleep apnea, obesity, excessive salt intake in salt-sensitive people, orthostatic hypotension, autonomic dysfunction, chronic renal disease, diabetic neuropathy, and old age[9]. According to the literature, night-time blood pressure is a stronger predictor of outcomes than daytime blood pressure, and patients with a lower night-time blood pressure reduction had a higher cardiovascular risk[2,9]. Surprisingly, there is some evidence that persons with significant night-time blood pressure dipping are at increased risk[15]. Non-dipper HT is related to an increase in end organ damage. In non-dipper HT, according to dipper HT; impaired cognitive functions, increased brain atrophy and silent cranial infarction, increase in renal albuminuria, low glomerular filtration rate and decrease in sodium excretion was reported[9,16-19].

Many small studies show a relationship between non-dipper HT and left ventricular hypertrophy (LVH), ventricular arrhythmia, and aortic dilatation[20-22]. Non-dipper HT is relevant to increased myocardial ischemia in patients with known CAD[23]. There is an increase in

Table 2. Routine laboratory examination of patient groups

	Dipper hypertension (n=49)	Non-dipper hypertension (n=109)	p-value
Creatinine, (mg/dL)			
Mean ± SD **Median (IQR)**	0.97±0.19 0.98 (0.26)	0.96±0.16 0.95 (0.21)	0.931
White blood cell, (10³ cells/µL)			
Mean ± SD **Median (IQR)**	8.06±1.73 7.60 (2.63)	7.47±1.95 7.20 (2.30)	**0.036**
Hemoglobin, (g/dL)			
Mean ± SD **Median (IQR)**	14.86±1.52 14.80 (2.30)	14.52±1.67 14.60 (2.40)	0.236
Platelet, (10³ cells/µL)			
Mean ± SD **Median (IQR)**	275.47±58.18 265.00 (61.00)	263.63±71.86 260.50 (88.75)	0.180
MPV, (fL)			
Mean ± SD **Median (IQR)**	9.12±1.07 9.10 (1.50)	9.39±1.27 9.25 (1.27)	0.211
RDW, (fL)			
Mean ± SD **Median (IQR)**	13.49±1.77 13.30 (0.85)	13.54±1.23 13.40 (1.00)	0.594
Total cholesterol, (mg/dL)			
Mean ± SD **Median (IQR)**	209.98±54.46 209.00 (64.50)	208.00±45.62 206.00 (55.50)	0.813
LDL cholesterol, (mg/dL)			
Mean ± SD **Median (IQR)**	130.39±47.44 124.00 (60.00)	128.35±40.71 131.00 (52.00)	0.784
Triglyceride, (mg/dL)			
Mean ± SD **Median (IQR)**	188.06±83.60 184.00 (119.50)	170.36±97.79 142.00 (102.00)	0.067
HDL cholesterol, (mg/dL)			
Mean ± SD **Median (IQR)**	43.14±8.84 41.00 (14.50)	47.90±11.52 46.00 (16.50)	0.14
Atherogenic index of plasma			
Mean ± SD **Median (IQR)**	0.250±0.262 0.233 (0.357)	0.141±0.262 0.111 (0.331)	**0.017**

Significant p-values are shown in bold.
MPV: Mean platelet volume, RDW: Red cell distribution width, LDL: Low density lipoprotein, HDL: High density lipoprotein, SD: Standard deviation, IQR: Interquartile range, n: Number

Table 3. Comparison of echocardiographic parameters of patient groups

	Dipper hypertension (n=49)	Non-dipper hypertension (n=109)	p-value
LVEF, %			
Mean ± SD **Median (IQR)**	64.09±5.48 65.00 (0)	63.30±6.65 65.00 (0.75)	0.477
LA diameter, (mm)			
Mean ± SD **Median (IQR)**	36.58±4.63 37.00 (5.00)	36.52±4.10 36.00 (5.00)	0.906
RWT, (fL)			
Mean ± SD **Median (IQR)**	0.41±0.10 0.40 (0.12)	0.51±0.52 0.44 (0.10)	0.80
Ascending aorta, (mm)			
Mean ± SD **Median (IQR)**	31.90±3.79 31.00 (4.75)	33.19±3.57 33.00 (4.00)	**0.049**

Significant p-values are shown in bold.
LVEF: Left ventricular ejection fraction, LA: Left atrium, RWT: Relative wall thickness, SD: Standard deviation, IQR: Interquartile range, n: Number

Table 4. The result of multivariate logistic regression analysis for the prediction of non-dipper hypertension

	Beta	Wald	p-value
Age	0.017	1.390	0.238
Diabetes mellitus	-1.274	3.500	0.061
Ascending aorta	0.118	2.274	0.132
Atherogenic index of plasma	-0.448	0.150	0.699
White blood cell	-0.092	0.599	0.439

cardiovascular morbidity in non-dipper HT in registry studies[1,9,24]. In all these studies, cardiovascular death or morbidity was the primary endpoint and the relationship between increased CAD or newly developing myocardial infarction and ABP has not been investigated.

The logarithm of the ratio of TG to HDL is used to measure the AIP[7,8]. A strong positive correlation was found between cholesterol esterification, lipoprotein particle size and apolipoprotein B extracted plasma[7,8]. CAD has been demonstrated to be a strong predictor in observational large case-control studies[8]. It is also related to increased all-cause death in elderly hypertensive women[25]. AIP has been proven as an independent marker of subclinical atherosclerosis in individuals with systemic lupus erythematosus[26].

The main purpose of this study was to research the association between AIP and dipper and non-dipper HT in hypertensive patients without known CAD. The AIP was significantly higher in dipper hypertensives than in non-dipper groups (0.250±0.262 vs. 0.141±0.262, p= 0.017). In previous studies, cardiovascular mortality and morbidity were higher in non-dipper HT individuals. However, in these studies, cardiovascular death was taken as the endpoint and no classification was made as death due to CAD or other cardiovascular causes. Non-dipper HT may increase cardiovascular deaths by causing cardiac hypertrophy and arrhythmias, without increasing CAD. As a matter of fact, there was no difference in coronary blood flow between non-dipper and dipper HT individuals in the previous coronary flow reserve study[27].

Additionally, inflammatory markers such as RDW and MPV, which are thought to be related to CAD in individuals with non-dipper HT, were highlighted to be higher in many studies. In our study, these marker levels were similar in both groups. Here, it may be thought that non-dipper status at similar inflammatory levels does not lead to an additional increase in CAD[11,12]. There are also data showing that non-dipper HT is not correlated with carotid intima media thickness and LV hypertrophy[28].

When the study groups were examined, it was observed that the rate of patients with DM was considerably higher in the dipper HT group. DM that has a definite relationship with atherosclerosis and TG levels Which is used calculating AIP, can be considered to cause a statistically significant increase in AIP in the dipper HT group.

In our study, relative wall thickness showing LV hypertrophy was similar in both groups. Although numerous studies have shown that the non-dipper HT group has a higher incidence of LV hypertrophy, this relationship is shown to be weak in this meta-analysis[29]. These results indicate that small scale studies in the literature can be influenced by many factors and may have opposite results. Large-scale randomized control studies and meta-analysis data are of utmost importance in decision making.

Study Limitations

The most important limitation of our study is that the frequency of DM was unevenly distributed among the groups, and it was higher in the dipper HT group. The fact that the study is not prospective and has small patient groups is other important limitation. Additionally, new methods such as 3-dimensional echocardiography or cardiac magnetic resonance imaging were not used to evaluate LVH. The use of AIP that is indirect indicator of atherosclerosis and affected by many variables is among the limitations of the study.

Conclusion

In our study, the AIP, which is an indicator of atherosclerosis, was highlighted to be related to dipper HT in ABP monitoring. This is the first study to investigate the correlation between ABP monitoring and AIP.

Ethics

Ethics Committee Approval: Gülhane School of Medicine Ethics Committee of the University of Health Sciences Turkey approved the study protocol (date: 25.09.2018, decision no: 18/217).

Informed Consent: Consent was obtained from all patients participating in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.A., M.Ç., U.Ç.Y., Design: S.A., Data Collection and/or Processing: Ö.E., H.T., Analysis and/ or Interpretation: V.Ö.B., Literature Search: S.A., V.Ö.B., M.Ç., Writing: S.A., U.Ç.Y.

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