Epicardial Fat Thickness and Neutrophil to Lymphocyte Ratio are Increased in Non-Dipper Hypertensive Patients

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BACKGROUND: In this study, we aimed to investigate the relationship between echocardiographic epicardial fat thickness (EFT), neutrophil to lymphocyte ratio (NLR; an important inflammatory marker), and diurnal blood pressure (BP) changes in patients with recently diagnosed essential hypertension.

METHODS: A total of 647 patients underwent echocardiography and 24 hours of ambulatory BP monitoring. EFT was measured by echocardiography, while NLR was measured by dividing the neutrophil count by the lymphocyte count. Patients were categorized into three groups according to BP pattern: the normotensive group, the dipper group, and the non-dipper group.

RESULTS: The mean EFT was highest in the non-dipper group (non-dipper group, 7.3 ± 3.0 mm; dipper group, 6.1 ± 2.0 mm; control group, 5.6 ± 2.0 mm; p < 0.001). NLR was also highest in the non-dipper group (non-dipper, 2.75 ± 2.81; dipper, 2.01 ± 1.32; control, 1.92 ± 1.11; p < 0.001). EFT was significantly correlated with age (r = 0.160, p < 0.001) and NLR (r = 0.353, p < 0.001). Furthermore, an EFT ≥ 7.0 mm was associated with the non-dipper BP pattern with 51.3% sensitivity and 71.6% specificity [95% confidence interval (CI) = 0.56–0.65, p < 0.001]. In a multivariate analysis, EFT [adjusted odds ratio (OR) = 3.99, 95% CI = 1.22–13.10, p = 0.022] and NLR (OR = 1.34, 95% CI = 1.05–1.71, p = 0.018) were independent parameters that distinguished a non-dipper pattern after adjustment for cardiovascular risk factors.

CONCLUSION: EFT and NLR are independently associated with impaired diurnal BP profiles in hypertensive individuals. EFT (as measured by echocardiography) and NLR appear to be helpful in stratifying cardiometabolic risk.

KEY WORDS: Epicardial fat thickness · Neutrophil to lymphocyte ratio · Hypertension · Non-dipper.
ic inflammation as assessed by NLR in patients with hypertension has not been well-studied. Thus, we aimed to investigate the association between EFT and NLR in patients with hypertension based on circadian BP variation.

METHODS

STUDY POPULATION

This cross-sectional, observational, single-center cohort study included 647 consecutive patients who simultaneously underwent 24-hour ambulatory BP monitor (ABPM) and echocardiography between January 2010 and March 2015. We included patients with normal renal function who were between 18–80 years of age. Patients with systemic inflammatory diseases, significant hepatic or renal dysfunction, neurologic disorders, secondary hypertension, valvular heart disease, atrial fibrillation, a history of heart failure, a history of acute coronary syndrome, or systemic or local malignancies were not included in the study. Demographic characteristics recorded at the first visit included age, sex, height, weight, current medications, smoking history, and other current diseases. Body mass index (BMI) was calculated as the ratio of dry weight in kilograms to height squared (in meters). This study was approved by the Institutional Review Board. All patients were required to provide written informed consent to participate.

LABORATORY ANALYSIS

Complete blood cell counts including total white blood cells (neutrophils and lymphocytes) and high sensitivity C-reactive protein (hs-CRP) were obtained at the first visit. Total serum uric acid were also measured. The NLR was calculated as the ratio of the neutrophil count to the lymphocyte count. Total serum protein (hs-CRP) were obtained at the first visit. Total serum uric acid were also measured. The NLR was calculated as the ratio of the neutrophil count to the lymphocyte count.

BLOOD PRESSURE MEASUREMENTS AND AMBULATORY BLOOD PRESSURE MONITORING

Office BP measurements were measured twice at five-min intervals using an automated office BP monitor (HBP-1100-E, OMRON Healthcare, Hoofddorp, the Netherlands). Noninvasive 24-h ABPM was performed on each patient’s non-dominant arm using an automatic oscillometric device (TONO-PORT V, PAR Medizintechnik, Berlin, Germany) on a normal working day. Patients were generally asked to refrain from intense exercise and to stop taking antihypertensive medications 24 hours prior to the office visit. All subjects were instructed to rest or sleep between 10:00 PM and 7:00 AM (nighttime) and to continue their usual activities between 7:00 AM and 10:00 PM (daytime). The accuracy of the device was checked against the standard auscultatory method to ensure that the difference in BP measurements between methods did not exceed 5 mm Hg. The device was set to obtain BP readings at 20-min intervals during the daytime and 40-min intervals during the nighttime. Only 24-hour recordings that included at least 80% successful recordings were accepted as valid. Each ABPM dataset was first automatically scanned to remove artifactual readings based on preselected editing criteria. The following ABPM parameters were evaluated: 24-hour mean systolic and diastolic BP levels, daytime mean systolic and diastolic BP levels, nighttime mean systolic and diastolic BP levels, and BP variability assessed by standard deviation (SD). Additionally, the magnitude of the nocturnal decline in BP (Δ nocturnal decline) was calculated as follows: daytime average BP - nighttime average; the percentage change in BP from day to night (% day - night BP) was calculated as: (daytime BP - nighttime BP) × 100 / daytime BP.

DIAGNOSIS OF HYPERTENSION

Following the recommendations of the European Society of Hypertension, a normotensive state was defined as a mean daytime ambulatory systolic and diastolic BP < 135/85 mm Hg and a mean nighttime ambulatory systolic and diastolic BP < 120/70 mm Hg by ABPM. True hypertension was diagnosed if the average daytime BP was higher than 135/85 mm Hg and the average nighttime BP was above 120/70 mm Hg. Because we divided groups by the ABPM parameter, masked hypertensive patients were assigned to the hypertensive group and white coat hypertension patients were assigned to the normotensive group. Hypertensive subjects who showed a < 10% reduction in BP from daytime to nighttime were defined as “non-dippers,” and those who had a reduction in BP ≥ 10% from daytime to nighttime were considered “dippers.” Patients were classified according to the ABPM.

ECHOCARDIOGRAPHIC MEASUREMENT

Standard 2-dimensional echocardiography was performed using a 3.5-MHz transducer (Philips iE33, Philips Medical Systems, Bothell, WA, USA) on all subjects while they were lying in the left lateral decubitus position, and examiners were blinded to patient information. Measurements of the thickness of the interventricular septum and posterior wall, the diameter of the left ventricle (LV) cavity, and the LV mass index (LVMi) were performed according to criteria outlined by the American Society of Echocardiography. Left atrial volume was measured by prolate ellipse methods. Echocardiographic assessments of EFT, defined as the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium, were measured perpendicularly from the free wall of the right ventricle at end-systole in three cardiac cycles as previously described. Because one of the critical issues in EFT measurement is the inconsistency in measurement location, the mean EFT was averaged from images of the parasternal long axis, parasternal short axis, and apical 4-chamber view. Offline measurement of EFT was performed by two cardiologists (KI Cho and BJ Kim) who were blinded to the clinical data. As previously described, the intra- and inter-observer variabilities

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of EFT were 3.3% and 5.8%, respectively.

**Statistical analysis**

Statistical analyses were performed with the commercially available computer program SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± SD for continuous variables and percentage (%) for categorical data. The Mann-Whitney U test was used for continuous variables and the chi-square test was used for categorical data. The normality of data was tested using the Kolmogorov-Smirnov test. Parameter differences among the 3 groups were evaluated using a one-way ANOVA for normally distributed variables or the Kruskal-Wallis test for non-normally distributed variables. Relationships between variables were examined with Pearson correlation coefficients. The cutoff values of EFT and NLR for predicting non-dippers with corresponding sensitivity and specificity were estimated by receiver operator characteristic (ROC) curve analysis. Multivariate logistic regression models for non-dippers were designed to determine the variables independently associated with this status. A two-tailed $p$-value < 0.05 was considered statistically significant.

**Results**

**Comparison of clinical and ambulatory blood pressure monitoring parameters**

A total of 353 hypertensive patients and 112 normotensive patients were analyzed, and their clinical features and ambulatory BP parameters according to diurnal variation are shown in Tables 1 and 2. NLR was the highest in the non-dippers compared to the other two groups (non-dipper, 2.75 ± 2.81; dipper, 2.01 ± 1.32; control, 1.92 ± 1.11; $p < 0.001$) (Table 1.

| Table 1. Baseline clinical and laboratory characteristics according to the diurnal variation |
|---------------------------------------------------------------|
| Control (n = 112) | Dipper (n = 269) | Non-dipper (n = 266) | $p$-value (ANOVA) |
|-------------------|------------------|----------------------|------------------|
| Age, years        | 52.7 ± 13.6      | 51.4 ± 13.3          | 51.6 ± 14.2      | 0.492 |
| Female gender, n (%) | 59 (53)          | 115 (43)             | 133 (50)         | 0.116 |
| Body mass index, kg/m² | 23.1 ± 3.1 | 24.5 ± 3.2           | 25.4 ± 4.2*      | 0.001 |
| Office systolic BP, mm Hg | 129.4 ± 17.4 | 131.9 ± 17.2         | 131.2 ± 18.1     | 0.473 |
| Office diastolic BP, mm Hg | 77.6 ± 13.7 | 78.3 ± 14.6          | 79.3 ± 14.0      | 0.505 |
| Heart rate, bpm   | 64.5 ± 13.3      | 65.8 ± 9.6           | 68.2 ± 12.5*     | 0.035 |
| Current smoking, n (%) | 8 (7)           | 19 (7)               | 18 (7)           | 0.104 |
| Diabetes, n (%)   | 8 (7)            | 16 (7)               | 20 (7)           | 0.768 |
| Dyslipidemia, n (%) | 17 (7)          | 82 (30)              | 91 (30)          | 0.080 |
| Previous BP medication, n (%) | -              | 55 (20)              | 57 (19)          | 0.431 |
| RAS blockade      | -                | 33 (12)              | 48 (16)          | 0.040 |
| Beta blocker      | -                | 50 (19)              | 57 (19)          | 0.237 |
| Calcium channel blocker | -            | 15 (6)               | 25 (8)           | 0.064 |
| Uric acid, mg/L   | 5.2 ± 1.6        | 5.6 ± 1.5            | 5.6 ± 1.4        | 0.158 |
| Creatinine, mg/dL | 0.75 ± 0.20      | 0.92 ± 0.81          | 1.04 ± 1.01      | 0.002 |
| Fasting glucose, mg/dL | 99.9 ± 14.7 | 101.0 ± 24.7         | 103.0 ± 21.7     | 0.645 |
| Total cholesterol, mg/dL | 184.7 ± 43.6 | 190.1 ± 38.5         | 179.1 ± 39.4     | 0.015 |
| LDL cholesterol, mg/dL | 106.3 ± 39.2 | 102.8 ± 34.7         | 110.9 ± 33.4     | 0.063 |
| HDL cholesterol, mg/dL | 50.4 ± 13.5 | 49.0 ± 12.4          | 48.7 ± 13.5      | 0.411 |
| Triglycerides, mg/dL | 131.9 ± 65.9 | 141.5 ± 95.9         | 136.9 ± 83.6     | 0.660 |
| hs-CRP, mg/dL     | 0.12 ± 0.23     | 0.25 ± 0.91          | 0.43 ± 1.18      | 0.048 |
| White blood cells, 10³/μL | 677.4 ± 2176 | 6906 ± 2174          | 7351 ± 2475     | 0.032 |
| Neutrophil        | 57.0 ± 11.5      | 56.2 ± 10.7          | 59.6 ± 11.9*     | 0.005 |
| Lymphocyte        | 33.1 ± 10.0      | 33.9 ± 9.8           | 30.5 ± 11.2*     | 0.002 |
| Eosinophil        | 2.5 ± 3.4        | 2.3 ± 1.8            | 2.4 ± 2.1        | 0.794 |
| Monocyte          | 6.6 ± 1.8        | 6.8 ± 1.9            | 6.97 ± 2.4       | 0.336 |
| Neutrophil to lymphocyte ratio | 1.75 ± 1.77 | 2.02 ± 1.32*         | 2.91 ± 3.04*     | < 0.001 |
| Hemoglobin, g/dL  | 13.4 ± 1.44      | 14.1 ± 1.59*         | 13.7 ± 1.67*     | 0.001 |
| Hematocrit, %     | 39.6 ± 4.24      | 41.4 ± 4.74          | 40.2 ± 4.90      | 0.001 |
| Platelets, 10³/μL | 223.5 ± 45.8     | 225.5 ± 54.9         | 232.3 ± 62.1     | 0.193 |

All values are presented as the mean ± SD. *$p < 0.05$ vs. normotensive control group, †$p < 0.05$ vs. dipper group. BP: blood pressure, RAS: renin angiotensin system, LDL: low density lipoprotein, HDL: high density lipoprotein, hs-CRP: high sensitivity C-reactive protein.
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The non-dipper group included more females and more patients on beta-blockers (all \( p < 0.05 \)). Circadian BP profiles and BP variability assessed by 24-hour mean BP SD were greater in hypertensive patients, especially in dippers (all \( p < 0.05 \)) (Table 2).

### Comparison of Echocardiographic Parameters

Although there was no significant difference in systolic function, hypertensive patients showed significantly greater wall thickness, greater LVMI, and a larger left atrial diameter, all of which were more prominent among non-dippers (Table 3). The mean EFT was significantly higher in both hypertensive groups compared to the control group and was highest in the non-dipper group (non-dipper group, 7.3 ± 3.0 mm; dipper group, 6.1 ± 2.0 mm; control group, 5.6 ± 2.0 mm; \( p < 0.001 \)) (Table 3, Fig. 1B).

### Correlations between EFT, NLR, and Clinical Parameters

EFT was significantly correlated with age (\( r = 0.160, p < 0.001 \)) (Fig. 2A), BMI (\( r = 0.091, p = 0.042 \)) (Fig. 2B), 24-hour mean BP variability (\( r = 0.152, p = 0.001 \)) (Fig. 2C), and NLR (\( r = 0.353, p < 0.001 \)) (Fig. 2D). NLR was also significantly correlated with 24-hour mean BP variability (\( r = 0.270, p < 0.001 \)).

Furthermore, an EFT \( \geq 7.0 \text{ mm} \) was associated with the non-dipper BP pattern with 51.3% sensitivity and 71.6% specificity (ROC area under curve of 0.606, 95% confidence interval (CI) 0.56–0.65, \( p < 0.001 \)) (Fig. 3A). And NLR \( \geq 2.1 \) was also associated with non-dipper BP pattern with 52.2% sensitivity and 65.3% specificity (ROC area under curve of 0.596, 95% CI 0.55–0.64, \( p < 0.001 \)) (Fig. 3B).

In multivariate analysis, EFT [adjusted odds ratio (OR) = 3.985, 95% CI = 1.215–13.066, \( p = 0.022 \)] and NLR (OR = 1.341, 95% CI = 1.052–1.710, \( p = 0.018 \)) were independent parameters that distinguished the non-dipper pattern after ad-

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**Table 2.** Comparison of parameters of 24-hour ambulatory BP monitoring according to the diurnal variation

|                      | Control (n = 112) | Dipper (n = 269) | Non-dipper (n = 266) | \( p \)-value (ANOVA) |
|----------------------|------------------|-----------------|----------------------|-----------------------|
| 24 mean BP variation | 11.5 ± 3.5       | 14.0 ± 4.3*     | 13.0 ± 4.6*          | < 0.001               |
| Day-night BP difference | -7.59 ± 6.48  | -11.4 ± 5.50*   | -3.2 ± 5.87*         | < 0.001               |
| 24-hour SBP, mm Hg   | 120.4 ± 9.84     | 138.8 ± 11.7*   | 141.2 ± 16.2*        | < 0.001               |
| 24-hour DBP, mm Hg   | 75.7 ± 5.98      | 89.1 ± 12.1*    | 89.5 ± 9.73*         | < 0.001               |
| 24-hour systolic SD, mm Hg | 13.6 ± 3.71 | 15.9 ± 4.28*†  | 14.9 ± 4.43*         | < 0.001               |
| 24-hour diastolic SD, mm Hg | 11.2 ± 3.52 | 13.7 ± 4.48*†  | 12.5 ± 4.41*         | < 0.001               |
| 24-hour mean BP, mm Hg | 90.3 ± 6.85     | 105.6 ± 9.88*   | 106.1 ± 13.0*†       | < 0.001               |
| 24-hour mean HR      | 71.1 ± 8.33      | 74.2 ± 10.5*    | 73.9 ± 11.4*         | 0.029                 |
| 24-hour mean HR SD   | 14.5 ± 6.06      | 15.7 ± 6.09     | 14.6 ± 7.73          | 0.141                 |

All values are presented as the mean ± SD. *\( p < 0.05 \) vs. normotensive control group, †\( p < 0.05 \) vs. dipper group. BP: blood pressure, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, SD: standard deviation

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**Fig. 1.** Comparison of NLR and EFT on circadian BP pattern. A: NLR was the highest in the non-dippers compared to the other two groups (non-dipper, 2.75 ± 2.81; dipper, 2.01 ± 1.32; control, 1.92 ± 1.11; \( p < 0.001 \)). B: The mean EFT was significantly higher in both hypertensive groups compared to the control group and was highest in the non-dipper group (non-dipper group, 7.3 ± 3.0 mm; dipper group, 6.1 ± 2.0 mm; control group, 5.6 ± 2.0 mm; \( p < 0.001 \)). NLR: neutrophil to lymphocyte ratio, BP: blood pressure, EFT: epicardial fat thickness.
justment for CV risk factors (Table 4).

**Discussion**

In the present study, we investigated the association between EFT and NLR as systemic inflammatory markers in hypertensive patients based on diurnal variation. The most unique findings obtained from this study are as follows: 1) EFT and NLR were highest in the non-dipper group, 2) there was a significant correlation between EFT and NLR, 3) EFT and NLR were highest in the non-dipper group, 2) there is a strong relationship between EFT and inflammation, EFT might be an associated inflammatory marker in patients with hypertension.

There are many data regarding other inflammatory markers related to CV outcomes, and there are contradictory reports regarding the association between NLR and clinical outcomes of CV disease. NLR might be just a marker reflecting the existence of epicardial fat and inflammation. Given the strong relationship between EFT and inflammation, EFT might be an associated inflammatory marker in patients with hypertension.

hs-CRP is also an important inflammatory marker which is widely used to assess CV risk. According to previous studies, both NLR and hs-CRP are important inflammatory markers, and there are significant correlations between these parameters. However, in our study, hs-CRP was not a significant inflammatory marker in non-dipping hypertension. Because our study represents a cross-sectional analysis, the exact mechanism is beyond our explanation. However, each of the many mechanistic factors in systemic inflammation may reflect different patterns of disease. A recent study also showed that NLR and hs-CRP may play different roles in various CV diseases. Our previous study showed that NLR, but not hs-CRP, was a predictive risk marker for significant coronary artery disease and carotid atherosclerosis. In addition, Gibson et al.
suggested that NLR, but not hs-CRP, was a predictor of new-onset atrial fibrillation after coronary artery bypass grafting. Consequently, increased EFT was independently associated with impaired diurnal BP profiles in individuals with hypertension resulting from autonomic dysfunction, sympathetic overactivity, and inflammation. The lack of decrease in nocturnal BP, known as non-dipping, is associated with lower adiponectin levels than measured in hypertensive dippers as well as an increased risk of CV events. In our results, EFT and NLR were greatest in patients with a non-dipping BP pattern,

**Fig. 2.** Correlations between EFT, NLR, and clinical parameters. EFT was significantly correlated with age \( (r = 0.160, p < 0.001) \) (A), body mass index \( (r = 0.091, p = 0.042) \) (B), 24-hour mean BP variability \( (r = 0.152, p = 0.001) \) (C), and NLR \( (r = 0.353, p < 0.001) \) (D). NLR was also significantly correlated with 24-hour mean BP variability \( (r = 0.270, p = 0.001) \) (E). EFT: epicardial fat thickness, NLR: neutrophil to lymphocyte ratio, BP: blood pressure.
and there was a significant correlation between EFT and NLR ($r = 0.353$), as expected. Moreover, EFT and NLR were significantly correlated with 24-hour mean systolic/diastolic BP variability and were independent parameters identifying the non-dipping pattern in patients with hypertension. This suggests a link between epicardial fat, inflammation, and autonomic dysregulation in hypertension.

Our study has several limitations. First, the retrospective design at a single institution may have led to selection bias. Second, previous hypertensive medications might have an important impact on BP variability. In order to account for these possible confounding effects, we performed sensitivity analysis for binary regression according to the use or non-use of medications and did not observe different results. Third, with no follow-up NLR data, we were limited in our ability to predict long-term outcomes. Finally, EFT can be affected by metabol-

| Table 4. Binary logistic regression analysis to identify the independent determinants of nocturnal non-dipping BP pattern |
|---------------------------------------------------------------|
| **Univariate** | **Odds ratio** | **95% CI** | **p-value** | **Multivariate** | **Odds ratio** | **95% CI** | **p-value** |
| Age | 1.001 | 0.989–1.013 | 0.877 | 1.868 | 1.027–3.399 | 0.041 |
| Female gender | 1.339 | 0.952–1.883 | 0.093 | | | |
| BMI | 1.061 | 0.974–1.157 | 0.177 | | | |
| Creatinine | 1.472 | 1.013–2.138 | 0.042 | | | |
| Mean SBP | 1.012 | 0.999–1.024 | 0.061 | | | |
| Mean HR | 0.997 | 0.982–1.013 | 0.741 | | | |
| 24-hour BP SD | 0.949 | 0.912–0.987 | 0.009 | | | |
| Total cholesterol | 0.993 | 0.988–0.998 | 0.005 | | | |
| NLR | 1.237 | 1.105–1.384 | < 0.001 | 1.341 | 1.052–1.710 | 0.018 |
| EFT | 3.869 | 2.635–13.070 | < 0.001 | 3.985 | 1.215–13.066 | 0.022 |
| hs-CRP | 1.203 | 0.940–1.539 | 0.142 | | | |
| LA volume | 1.046 | 1.013–1.079 | 0.005 | 1.001 | 0.951–1.053 | 0.982 |
| Ee | 1.131 | 1.069–1.196 | < 0.001 | 1.135 | 1.033–1.247 | 0.009 |
| LVMI | 2.292 | 0.487–10.780 | 0.294 | | | |
| RWT | 1.001 | 0.989–1.013 | 0.877 | | | |

BMI: body mass index, SBP: systolic blood pressure, HR: heart rate, BP: blood pressure, SD: standard deviation, NLR: neutrophil to lymphocyte ratio, EFT: epicardial fat thickness, hs-CRP: high sensitivity C-reactive protein, LA: left atrial, LVMI: left ventricular mass index, RWT: relative wall thickness, Ee: peak early diastolic mitral filling velocity, Ea: mitral annular velocity, CI: confidence interval.
ic syndrome; however, we did not measure the waist circumference of enrolled patients, so we could not classify or analyze metabolic syndrome in our patients. However, based on the significant correlations between 24-hour mean systolic BP, EFT and obesity (as represented by BMI or EFT) we posit a possible association with metabolic syndrome. Therefore, a larger, prospective study is required to confirm our findings.

In conclusion, EFT, an indicator of cardiac autonomic activity, was greatest in hypertensive patients with a non-dipping pattern, and increased NLR, an indicator of inflammation, was observed in hypertensive patients regardless of nocturnal BP pattern. EFT and NLR were independently associated with impaired diurnal BP profiles in hypertensive individuals. EFT and NLR appear to be helpful in cardiometabolic risk stratification. The association between EFT and adverse CV outcomes in patients with increased NLR needs to be investigated in further detail in future research.

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