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Original Article

The effect of cardiac rehabilitation on inflammatory parameters in non-dipper hypertensive patients

Non-dipper hipertansif hastalarda kardiyak rehabilitasyonun inflamatuvar parametrelere etkisi

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Abstract

Aim: Non-dipping pattern in blood pressure increases the risk of cardiovascular diseases in hypertensive patients. Inflammation is responsible for the etiopathogenesis of cardiovascular disease and non-dipper hypertension. We aimed to determine the effect of cardiac rehabilitation on inflammatory parameters in non-dipper hypertensive patients.

Material and Methods: Medically treated 56 dipper hypertensive patients were compared with 58 non-dipper hypertensive patients in terms of clinical and demographic features. All non-dipper hypertensive patients were referred to the cardiac rehabilitation program for 16-week duration. As inflammatory parameters, C-reactive protein (CRP) and neutrophil-lymphocyte ratio (NLR) were measured before and after cardiac rehabilitation. At the end of cardiac rehabilitation 24-h ambulatory blood pressure monitoring was repeated and diurnal variation was analyzed.

Results: No significant difference was found between dippers and non-dippers in terms of age, gender, daytime systolic and diastolic blood pressure, while nighttime systolic and diastolic blood pressure was higher in non-dippers. Baseline inflammatory markers such as CRP (0.46±0.19 vs. 0.38±0.19) and NLR (2.21±0.69 vs. 1.82±0.69) were found higher in non-dippers than in dippers (P=0.019 and P=0.004, respectively). After the cardiac rehabilitation program, both CRP (0.46±0.19 vs. 0.41±0.16; P=0.012) and NLR (2.21±0.69 vs. 2.07±0.66; P=0.005) significantly decreased in non-dippers. Cardiac rehabilitation program had no effect on the diurnal variation of blood pressure in non-dippers. Out of 58 non-dippers, six patients transformed from non-dipper to dipper pattern after cardiac rehabilitation.

Conclusion: This study showed that cardiac rehabilitation reduces the inflammatory parameters that constitute the cardiovascular risk markers in non-dipper hypertensive patients.

Keywords: Ambulatory blood pressure monitoring; cardiac rehabilitation; hypertension; inflammatory markers; non-dipper hypertension

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Öz

Amaç: Hipertansif hastalarda kan basıncının düşmemesinin kardiyovasküler hastalık riskini artırdığı gösterilmiştir. İnflamasyonun kardiyovasküler hastalık ve dipper olmayan hipertansiyonun etiyopatogenezinden sorumlu olduğu bilinmektedir. Dipper olmayan hipertansif hastalarda kardiyak rehabilitasyonun inflamatuvar parametrelere etkisini belirlemeyi amaçladık.

Gereç ve Yöntemler: Tıbbi tedavi gören 56 dipper hipertansif hasta, klinik ve demografik özellikler açısından 58 dipper olmayan hipertansif hasta ile karşılaştırıldı. Dipper olmayan tüm hipertansif hastalar 16 haftalık kardiyak rehabilitasyon programına sevk edildi. İnflamatuvar parametreler olarak, C-reaktif protein (CRP) ve nötrofil-lenfosit oranı (NLR) kardiyak rehabilitasyondan önce ve sonra ölçüldü. Kardiyak rehabilitasyonun sonunda 24 saatlik ambulatuvar kan basıncı monitörizasyonu tekrarlandı ve diürnal varyasyon analiz edildi.

Bulgular: Yaş, cinsiyet, gündüz sistolik ve diyastolik kan basıncı açısından dipper ve dipper olmayanlar arasında anlamlı fark bulunmazken, dipper olmayanlarda gece sistolik ve diyastolik kan basıncı daha yüksekti. İnflamatuar belirteçler olarak başlangıç CRP (0,46 ± 0,19'a karşı 0,38 ± 0,19) ve NLR (2,21 ± 0,69'a karşılık 1,82 ± 0,69) dipperlere kıyasla dipper olmayanlarda daha yüksek bulunmuştur (sırasıyla P = 0,019 ve P = 0,004). Kardiyak rehabilitasyon programından sonra, hem CRP (0.46 ± 0.19'a karşı 0.41 ± 0.16; P = 0.012) hem de NLR (2.21 ± 0.69'a karşı 2.07 ± 0.66; P = 0.005) dipper olmayanlarda önemli ölçüde azaldı. Kardiyak rehabilitasyon programının, dipper olmayanlarda kan basıncının günlük değişimleri üzerinde hiçbir etkisi yoktu. Dipper olmayan 58 kişiden 6'sı, kardiyak rehabilitasyondan sonra dipper olmayan modelden dipper paterne dönüştü.

Sonuç: Bu çalışma, kardiyak rehabilitasyonun dipper olmayan hipertansif hastalarda kardiyovasküler risk belirteçlerini oluşturan inflamatuvar parametreleri azaltabileceğini göstermiştir.

Anahtar kelimeler: Ambulatuvar kan basıncı monitorizasyonu; kardiyak rehabilitasyon; hipertansiyon; inflamatuvar belirteçler; non-dipper hipertansiyon

Introduction

Systemic blood pressure (BP) has a circadian rhythm characterized by higher values in the morning and marked decrease during sleep at least 10-20% of daytime value. Less than a 10% nocturnal decrease in systolic and diastolic blood pressure compared to daytime values is called the non-dipping pattern.[1] Non-dipper hypertensive patients have an increased risk of cardiovascular events.[2] Previous studies examined the effect of aerobic exercise on blood pressure in non-dipper hypertensive patients.[3,4]

Inflammation is responsible for the etiopathogenesis of both cardiovascular events and non-dipper hypertension.[5-7] Regular exercise programs can improve cardiovascular health in non-dipper hypertensive patients by helping reduce inflammatory markers. Cardiac rehabilitation (CR) is a graded exercise program tailored to the patient's preferences, possibilities, and physiologic reserve. Despite being safe, effective, and a guideline-recommended treatment to improve the quality of life, exercise training remains grossly underutilized. Cardiac rehabilitation improves prognosis in addition to cardiac functions and exercise capacity in patients with cardiovascular diseases.[8] The effect of exercise on inflammatory markers depends on the duration and intensity of the exercise and the patient's characteristics.[9] Therefore, this study aimed to examine the effect of CR programs on inflammatory markers in non-dipper hypertensive patients.

Materials and Methods

Population of the Study

The study was conducted between November 2018 and March 2019 and the 24-hour (h) ambulatory blood pressure measurement (ABPM) was performed on all hypertensive patients. From 24h ABPM database of our institution, 56 dipper hypertensive patients and 65 non-dipper hypertensive patients were recruited to study after getting informed consent. All non-dipper patients were referred to a 16-week CR program. Patients who will not be admitted to CR program were excluded from the study (Figure1). Dipper hypertensive patients were excluded from the CR program. The body mass index (BMI) was calculated as weight (kg)/height (m2) for all patients. All patients were taking antihypertensive therapy (angiotensin-converting

enzyme inhibitors, or angiotensin II receptor blockers or Ca-channel blockers) for at least three months before the study. The 24-hour noninvasive ABPM allows the detection of blood pressure (BP) circadian rhythm and dipping or non-dipping pattern. The 24-h ABPM and BMI measurements were repeated for all non-dipper patients 24 h after the completion of the 16-week CR program. The 24-h ABPM was performed using a mobile compact digital recorder (Delmar Reynolds, Tracker NIBM2, Hertford, the United Kingdom).

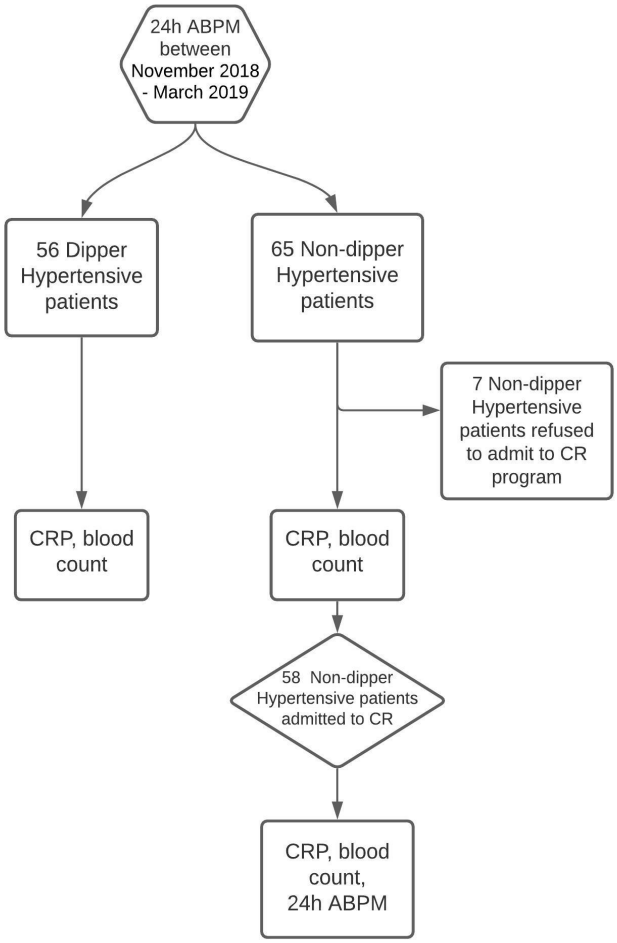

Figure 1. Study Protocol

This study was approved by Ethics Committee of the Haydarpasa Numune Research and Training Hospital,Research and Ethic Committee on 22.10.2018 with the number of 2018/63. Informed consent was taken from the patients enrolled in this study. The study was carried in compliance with the Declaration of Helsinki.

Exclusion Criteria

Patients who had previous cardiovascular disease, electrocardiographic evidence of cardiac arrhythmias, clinical and echocardiographic evidence of heart failure (EF<50%), patients with stage ≥2 hypertension, diabetes mellitus, and chronic kidney disease with a glomerular filtration rate of <60 ml/min 1.73m2, inflammatory-rheumatologic diseases were excluded from the study.

Biochemical and Hematological Laboratory Findings

C-reactive protein values (CRP) were measured before and after the CR program. The reference value for CRP was 0–0.5 mg/dl. Fasting venous blood samples were collected in pre-cooled 4.9 ml EDTA monovets. Blood samples were collected at the beginning of the program and were repeated within 48–72 h after the completion of CR program. The analysis was conducted with an automatic cell counter (Sysmex XN-450; Nordestedt, Germany). Hematological parameters (hemoglobin (HGB), white blood cell (WBC), neutrophil, lymphocyte, monocyte and platelet counts were analyzed. The neutrophil-lymphocyte ratio (NLR) was calculated by dividing the number of neutrophils into the number of lymphocytes.

Cardiac Rehabilitation Program

This program was conducted in the CR unit of our hospital. All non-dipper hypertensive patients were admitted to a 16-week moderate-intensity aerobic exercise program adapted to their comorbidities and physical limitations. First, all eligible patients took a submaximal cycle ergometer test. The exercise program was tailored for each individual patient according to their test results. For this program, 40%-60% of patient maximal exercise capacity was calculated according to their comorbidities and an interval training aerobic exercise program was uploaded to the cardiac rehabilitation cycle ergometers for each patient. The intensity of exercise was determined by Karvonen formula (10). The target heart rate (HR) for 40%-60% (moderate) intensity program was calculated as a [(40%-60%) X (max HR – Resting HR) + (Resting HR)]. The frequency of exercise was gradually increased. First, each program included 60-minute aerobic exercise sessions on a cycle ergometer twice a week at 40%-60% of each patient's maximal exercise capacity for the first 4 weeks. Then the frequency was increased to three times a week at 40%-60% of maximal capacity for the remaining 12 weeks. Each program included 60-minute aerobic exercise sessions with a 5-minute warm-up, 50-minute active phase, and 5-minute cool-down. On each session, cardiac rehabilitation nurses evaluated patients' Borg scale. By adjusting their program, it was ensured that patients remained at an 11–13 rating of

perceived exertion on the 6–20 Borg Scale.[11] All exercises were planned and supervised by physiotherapist.

Statistical Analysis

Continuous (non-categorical) variables were expressed as ± SD while categorical variables were expressed as percentages. Kolmogorov–Smirnov and Levene tests were performed to test the normal distribution of variables. Chi-square test or Fisher's exact test was used for categorical variables depending on the estimated cell value. For non-categorical variables, Student's t-test was used wherever possible, while Mann Whitney U test was used when the data did not show normal distribution. The paired t-test was used for repetitive measurements of continuous variables. Pearson correlation analysis was done between variables. Statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA) program.

Results

No significant difference was found between the dippers and non-dippers in terms of age, gender, daytime and nighttime heart rate, daytime systolic blood pressure (SBP), daytime diastolic blood pressure (DBP), and BMI (P=0.786; P=0.717; P=0.063; P=0.898; P=0.691; P=0.202; P=0.076, respectively). However, it was observed that nighttime SBP and nighttime DBP were significantly higher in non-dippers than in dippers (P<0.001 for both) (Table 1).

Table 1. Clinical characteristic data in Dipper and Non-Dipper Hypertensive patients

Variables	Dipper Hypertensive Patients (n=56)	Non-dipper Hipertensive Patients (n=58)	P
Age	56±7.80	56±8.42	0.786
Male gender (n, %)	27 (48.2)	26 (44.8)	0.717
Daytime heart rate (beats/min)	80.48±3.96	79.06±4.06	0.063
Nighttime heart rate (beats/min)	71.76±3.39	71.86±4.37	0.898
Daytime SBP (mmhg)	137.69±6.43	138.18±6.76	0.691
Daytime DBP (mmhg)	89.16±3.65	90.01±3.46	0.202
Nighttime SBP (mmhg)	121.92±5.83	132.05±6.58	<0.001
Nighttime DBP (mmhg)	77.51±3.33	85.00±3.34	<0.001
BMI	25.59±1.96	26.30±2.22	0.076
ACEi (n, %)	23 (41.1)	23 (39.7)	0.878
ARB (n, %)	19 (33.9)	18 (31.0)	0.741
Ca Channel Blocker (n, %)	14 (25.0)	17 (29.3)	0.605

Data are given as mean ± SD, n (%); min: Minute; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index, ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker

There was no significant difference between dippers and non-dippers in terms of WBC, HGB, and the numbers of platelets, neutrophils, and monocytes (Table 2). However, it was observed that the number of lymphocytes was significantly lower in non-dippers (P=0.001).

Table 2. Hematological and Inflammatory parameters in Dipper and Non-dipper hypertensive patients

Variables	Dipper hypertensive patients (n=56)	Non-dipper hipertensive patients (n=58)	P
CRP	0.38±0.19	0.46±0.19	0.019
WBC (K/uL)	7.69±1.48	7.46±1.62	0.434
HGB (g/dl)	12.92±1.29	12.91±1.25	0.951
PLT (K/uL)	247.44±37.61	242.01±37.90	0.444
Neutrophil (K/uL)	4.32±1.17	4.49±1.34	0.469
Lymphocyte (K/uL)	2.49±0.63	2.11±0.53	0.001
Monocyte (K/uL)	0.49±0.12	0.47±0.12	0.345
NLR	1.82±0.69	2.21±0.69	0.004

Data are given as mean ± SD, CRP: C-reactive protein; WBC: White blood cell; HGB: Hemoglobin; PLT: Platelet; NLR: Neutrophil lymphocyte ratio

Considering the comparison of two groups in terms of inflammatory parameters, CRP (0.38±0.19 vs. 0.46±0.19) and NLR (1.82±0.69 vs. 2.21±0.69) were found to be significantly higher in non-dippers (P=0.019, P=0.004, respectively) (Table 2).

Before and After the Cardiac Rehabilitation

Considering the 24-h ABPM after the 16-week CR program, there was no significant difference in BP parameters of non-dippers (P >0.05 for all) while daytime heart rate (HR) decreased significantly after CR (P<0.001) (Table 3). Out of 58 non-dipper hypertensive patients, only six patients (10.34%) transformed from non-dipper to dipper hypertension after CR. Additionally, the BMI values significantly decreased in non-dippers after CR (26.30±2.22 vs. 25.64±2.19, P<0.001).

Table 3. 24-hour Ambulatory BP monitoring in non-dipper hypertensive patients before and after CR

Variables	Pre CR (n=58)	Post CR (n=58)	P
Daytime heart rate (beats/min)	79.06±4.06	77.46±3.68	<0.001
Nighttime heart rate (beats/min)	71.86±4.37	71.41±3.62	0.072
Daytime SBP (mmhg)	138.18±6.76	137.56 ±5.89	0.054
Daytime DBP (mmhg)	90.01±3.46	89.74±3.38	0.103
Nighttime SBP (mmhg)	132.05±6.58	131.81±5.99	0.240
Nighttime DBP (mmhg)	85.00±3.34	84.81±3.34	0.296

Data are given as mean ± SD, CR: Cardiac rehabilitation; Min: minute; SBP: systolic blood pressure; DBP: diastolic blood pressure

Volume 12 Number 2 p: 140-146

The CRP (0.46±0.19 vs. 0.41±0.16) and NLR (2.21±0.69 vs. 2.07±0.66) significantly decreased after CR (P=0.012 and P=0.005, respectively) (Table 4). We found a moderate and positive correlation between CRP and NLR before and after CR (r=0.518; P<0.001 and r=0.575; P<0.001, respectively) (Table 5).

Table 4. Hematological and Inflammatory parameters in non-dipper hypertasive patients before and after CR

Variables	Pre-CR (n=58)	Post-CR (n=58)	P
BMI (kg/m2)	26.30±2.22	25.64±2.19	<0.001
CRP	0.46±0.19	0.41±0.16	0.012
WBC (K/uL)	7.46±1.62	7.38±1.56	0.245
HGB (g/dl)	12.91±1.25	12.98±1.13	0.444
PLT (K/uL)	242.01±37.90	250.41±40.29	0.162
Neutrophil (K/uL)	4.49±1.34	4.39±1.29	0.058
Lymphocyte (K/uL)	2.11±0.53	2.19±0.50	0.065
Monocyte (K/uL)	0.47±0.12	0.49±0.12	0.053
NLR	2.21±0.69	2.07±0.66	0.005

Data are given as mean ± SD, CR: Cardiac rehabilitation; BMI: Body mass index; CRP: C-reactive protein; WBC: white blood cell; HGB: Hemoglobin; PLT: platelet; NLR: neutrophil lymphocyte ratio

Table 5. Correlation analysis among CRP and NLR before and after CR

	Pre-CR NLR		Post-CR NLR	
	r*	P	r*	P
CRP	0.518	<0.001	0.575	<0.001

*Calculated using Pearson's correlation coefficient. CRP: C-reactive protein; NLR: Neutrophil lymphocyte ratio; CR: Cardiac rehabilitation

Discussion

In our study, the cardiac rehabilitation program had no effect on the dipping pattern of blood pressure. However, CRP and NLR as known to cause adverse cardiac effects were significantly decreased by CR.

With 16-week CR, we did not get any significant changes on diurnal blood pressure rhythm in non-dippers. Similarly, Nami et al. found that aerobic exercise training resulted in a blood pressure-lowering effect in dippers but failed in reducing diurnal and nocturnal blood pressure values in nondippers.[3] According to a meta-analysis by Cornelissen et al. aerobic exercise caused a significant decrease in the 24-h ABPM, daytime SBP and daytime DBP, while it had no effect on nighttime blood pressure parameters.[12] Sympathetic activity increases during the day and decreases at night, accompanied by an increase in parasympathetic activity at night.[13] In fact, decreasing BP parameters due to aerobic exercise can be associated with the reduction in daytime sympathetic activity or increase daytime parasympathetic activity with exercise.[14] However, aerobic exercise may not cause a significant change in nighttime BP parameters due to lower sympathetic nervous system activity at nighttime than a daytime.[15] Nevertheless, in our study aerobic exercise did not cause a significant change in daytime BP parameters. The difference between this study and their meta-analysis [12] can be related to different patient profiles. Because non-dipper patients were not evaluated in their meta-analysis.

According to hematological laboratory findings, numbers of WBC, neutrophils, monocytes, and platelets were similar between dippers and non-dippers in our study. However, the number of lymphocytes was significantly lower in non-dippers than in dippers. The hematological findings in this study were similar to the findings of the study by Sunbul et al. In their study, only the number of lymphocytes was significantly lower in non-dippers than in dippers.[7] But, they did not evaluate the hematological parameters after aerobic exercise. Barttlet et al. found that moderate-intensity aerobic exercise did not affect the total counts of WBC, neutrophil, lymphocyte, and monocyte in sedentary adults.[16] Moreover, moderate-intensity exercise did not cause a significant increase in the number of immune cells while improving immune cell activity.[16] Natural killer lymphocytes (NK) are an important component of the natural immune system. Nieman et al. showed that moderate-intensity exercise program improved the NK cell activity without increasing the number of NK cells.[17]

It has been shown that CRP, which is an indicator of inflammation, decreased after CR in patients with coronary arterial bypass operation.[18] It has been understood that CRP is an independent predictor of atherothrombotic risk related to cardiovascular events beyond being an inflammatory marker. Ermis et al. reported that CRP was significantly higher in non-dippers than in dippers like in our study.[6] However, they did not investigate CRP in non-dippers after aerobic exercise.[6] CRP significantly decreased in non-dippers after CR in our study. CRP is synthesized in the liver, smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipose tissue as a response to inflammatory cytokines.[19] The decrease in CRP levels this study might be associated with the effect of CR on adipose tissue. Previous studies showed that weight loss is significantly associated with reduced CRP.[20, 21] Similarly, BMI values decreased in non-dippers after CR in our study.

CRP level is sensitive to the severity of the inflammatory process and changes according to the degree of inflammation. Studies showed that there was an interaction between leptin

and CRP levels.[16, 22] It was shown that increased leptin levels increase CRP levels in the cell culture medium.[22] Another study was also reported that moderate-intensity exercise decreased leptin levels.[16] We postulate that CR might have decreased CRP levels by reducing leptin levels. Further studies can shed light on this subject.

It is known that NLR, which is an indicator of systemic inflammation, is associated with adverse cardiovascular events. Additionally, NLR also has an important role in risk stratification.[23] Previous studies showed that NLR was higher in non-dippers as in our study.[7] The lymphocyte counts decrease due to increased lymphocyte apoptosis as inflammation continues.[24] We speculate that, in our study, CR program decreases the inflammation that leads to mildly increment in lymphocyte counts and mildly decrement in neutrophils in non-dippers. Additionally, NLR significantly decreased in non-dippers after CR in our study. Thus, reduction of NLR without causing a significant change in immune cell counts in non-dippers could be evidence of suppression of inflammation by CR.

This study is a cross-sectional study with a relatively small sample size. We could not control confounding factors that could affect CRP and hematological parameters. So, our results should be verified in the multi-center prospective longitudinal studies with larger sample sizes. In addition, there is no follow-up for major adverse cardiac events. The limitations of this study should be considered while interpreting the results.

Conclusion

CRP is both a predictor of cardiovascular diseases and a prognostic marker in cardiovascular diseases in asymptomatic patients (25). Therefore, CRP plays a more important role than other inflammatory markers in cardiovascular diseases. Moreover, NLR is an important marker that plays a role in determining the prognosis of cardiovascular diseases. Increased NLR is associated with poor prognosis in cardiovascular diseases. While CR did not cause a significant change in BP parameters in non-dippers, it significantly decreased CRP and NLR of inflammatory markers. Cardiac rehabilitation might help reduce cardiovascular events by decreasing inflammatory markers in non-dipper hypertensive patients. Further studies can shed light on this matter.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest

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