# Cardiac Autonomic Impairment and Chronotropic Incompetence in Dipper and Nondipper Hypertension

## Dipper ve Non-Dipper Hipertansif Hastalarda Kardiyak Otonom Fonksiyonlarda Bozulma ve Kronotropik Yetersizlik

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**ABSTRACT Objective:** The aim of the present study was to compare the autonomic nervous system activity indexes obtained from treadmill exercise stress testing in dipper and non-dipper hypertensive patients. **Material and Methods:** This study included 214 hypertensive patients, under antihypertensive medication. All study participants underwent 24-hour ambulatory blood pressure monitoring (ABPM) and maximal exercise testing. Thereafter patients were divided into two groups: 94 dipper hypertensives and 120 non-dipper hypertensives. Heart-rate (HR) response during exercise was evaluated by the chronotropic index (CI). HR recovery (HRR) was defined as the difference between HR at peak exercise and first minute after the exercise test. **Results:** Daytime systolic and diastolic BP measurements were similar, however night-time measurements were significantly lower among dippers than non-dippers (night-time systolic BP: 114.1±11.4 vs 126.3±15.0 mmHg, p<0.001; night-time diastolic BP: 72.3±7.3 vs 79.9±9.8 mmHg, p<0.001). Chronotropic index was lower than normal in both groups (0.79±0.1 vs 0.78±0.7 p=NS). Dippers had higher HRR values than non-dippers (31.8±4.6 vs 29.1±4.6 p<0,001). HRR was positively correlated with the percentage decline of systolic and diastolic BP from day to night (r=0.255 p<0.001 and r=0.228 p=0.001, respectively). There were no correlation between CI and percentage of systolic and diastolic BP reduction from day to night (r=0.067 p>0.05 and r=0.16 p>0.05, respectively). **Conclusion:** Hypertensive patients have abnormal HR response to exercise,. Non-dippers had lower HRR values than dippers. This may due to a relative general decrease of parasympathetic reactivation after exercise that is linked to the failure of nighttime fall of BP.

**Key Words:** Hypertension; heart rate

**ÖZET Amaç:** Bu çalışmanın amacı dipper ve non-dipper hipertansif hastalarda egzersiz stres testi ile elde edilen otonom sinir sistem aktivite parametrelerinin karşılaştırılmasıdır. **Gereç ve Yöntemler:** Çalışmamıza medikal tedavi altında olan 214 hipertansif hasta alındı. Tüm hastalara 24 saat ambulatuvar kan basıncı monitorizasyonu ve egzersiz stres testi yapıldı. Hastalar dipper hipertansif (94 hasta) ve non-dipper hipertansif (120 hasta) olmak üzere iki gruba ayrıldı. Kronotropik indeks (KI) ve kalp hızı toparlanma (KHT) indeksi kaydedildi. **Bulgular:** Hastaların gün içinde ölçülen sistolik ve diyastolik kan basıncı (KB) değerleri arasında anlamlı fark bulunmadı, gece döneminde ölçülen KB değerleri dipper grubunda anlamlı olarak daha düşük bulundu ( gece dönemi sistolik KB: 114,1±11,4, 126,3±15,0 mmHg, p<0,001; gece dönemi diyastolik KB: 72,3±7,3, 79,9±9,8 mmHg, p<0,001). Her iki grupta da KI normalden düşük bulundu (0,79±0,1 ve 0,78±0,1 p=AD). Dipper hipertansifler, non-dipper hipertansiflere göre daha yüksek KHT indeksine sahiptiler (31,8±4,6 vs 29,1±4,6 p<0,001). KHT indeksi ile sistolik ve diyastolik KB değerlerinin gündüz-gece düşüş yüzdesi arasında anlamlı pozitif ilişkili bulundu (sırası ile r=0,255 p<0,001 ve r=0,228 p=0,001). KI ile sistolik ve diyastolik KB değerlerinin gündüz-gece düşüş yüzdesi arasında anlamlı bir ilişki saptanmadı (sırası ile r=0,067 p>0,05 ve r=0,16 p>0,05). **Sonuç:** Hipertansif hastalar egzersize anormal kalp hızı yanıtı vermektedirler. Non-dipper hipertansifler, dipper hipertansifler ile karşılaştırıldıklarında daha düşük KHT indeksine sahiptirler. Bu durum egzersiz sonrası parasempatik reaktivasyon bozukluğuna bağlı olabilir. Parasempatik reaktivasyonda gözlenen bu bozulma beklenen gece kan basıncı düşüşünün oluşmamasını açıklayabilir.

**Anahtar Kelimeler:** Hipertansiyon; kalp hızı

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Normally, blood pressure (BP) exhibits a circadian rhythm that decreases during sleep and increases during wakefullness.[1] The average systolic blood pressure (SBP) and diastolic blood pressure (DBP) difference between day and night is 10-20% this is referred to as dipping pattern. In some subjects whether they have normo- or hypertension this nocturnal BP decrease is lost and this condition referred as non-dipping pattern.[2] Mechanism of non-dipping pattern is not completly understood. Abnormal autonomic nervous system activity has been suggested as a possible mechanism of non-dipping phenomenon.[3] Non-dipper subjects have been reported to have increased cardiovascular morbidity and mortality.[4-6]

Exercise stress test variables, heart rate recovery (HRR) and chronotropic index (CI), have been shown to have prognostic value.[7] Both an attenuated heart rate (HR) response to exercise (chronotropic incompetence) and HRR after exercise has been considered to reflect cardiac autonomic functions and associated with increased mortality.[8-10]

Our aim was to examine the CI and HRR in patients with dipper versus non-dipper hypertension.

## MATERIAL AND METHODS

The study sample consisted of 214 hypertensive patients under medical treatment who underwent maximal exercise testing and ambulatory blood pressure monitorization at our cardiology clinic between January 2011 and January 2012. Istanbul University Institute of Cardiology Ethics Committee approved the study protocol and each subject were informed consent prior to enrollment. Information that was recorded at the time of the physical examination included previous myocardial infarction, hypercholesterolemia, diabetes mellitus, stroke, smoking status, antihypertensive drugs and cardiac arrhythmias. When suspected, special laboratory tests for secondary causes of hypertension were performed. Patients with secondary hypertension, left bundle branch block, congestive heart failure, cardiac valve diseases, conditions preventing technically adequate ambulatory blood pressure monitoring (ABPM) and major non-cardiovascular disease were excluded from the study. Twenty-four-hour ABPM was carried out on the non-dominant arm (PhysioQuant; Envitec, Germany). The device was set to obtain BP readings at 15 min intervals during the day (07:00-23:00 h) and at 20 min intervals during the night (23:00-07:00 h). Of the 116 hypertensive patients 94 of them were categorized as dippers, while the remaining 120 were categorized as non-dippers. Treadmill exercise stress testing was performed for all subjects according to Bruce protocol. β-blocker, calcium channel blockers was stopped 48 hours before treadmill exercise stress testing. Treadmill exercise stress test termination criteria was moderately severe angina, >2.0 mm abnormal ST depression, a sustained drop in systolic blood pressure, or serious rhythm disturbances.[11] BP was taken manually and exercise capacity (METs) was estimated using peak treadmill speed and grade. HR was measured standing, during each minute of exercise, at maximum exercise, and in recovery at 1 min. Maximum achievable heart rate (MHR) was calculated as 220 beats per minute-age in years and target heart rate was calculated as 85% of MHR. HRR was defined as (maximum heart rate-heart rate at 1 minute after exercise) and represented the drop in HR during that time interval. CI was calculated as [(HRpeak-HRrest)/(220-age-HRrest)]. Chronotropic index smaller than 0.8 was defined as chronotropic incompetence.[12,13]

### STATISTICAL ANALYSIS

Continuous variables were expressed as mean±SD. Categorical variables were expressed as percentages. Statistical analyses were performed SPSS 20 for windows (Inc., Chicago, IL, USA). Mean values for dipper and non-dipper patients were compared using Student's t-test for independent samples. Chi-square statistics were used to compare categorical variables between groups. The correlations between the observed variables were examined by Pearson's correlation test. p value <0.05 was considered statistically significant.

## RESULTS

On the basis of the results of ABPM, 120 subjects were classified as non-dipper hypertensive, 94 sub-

jects were classified as dipper hypertensive (Table 1). There were no significant differences in age, gender, smoking habit, hyperlipidemia, diabetes mellitus, ischemic heart disease and cerebrovascular disease between dippers and non-dippers. Left ventricular ejection fraction was normal in both groups. Patients had been treated with the following antihypertensive agents: β-blocker, diuretic, calcium channel blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. β-blocker and calcium channel blockers were stopped 48 hours before exercise stress testing. There were no differences in medication use between two groups.

There were no differences in SBP and DBP between the dippers and the non-dippers during the day. However, SBP and DBP were significantly higher among the non-dippers at night (Table 2).

The resting heart rate, maximal heart rate, duration of exercise, metabolic equivalents achieved during exercise stress test, maximal systolic and diastolic blood pressures were similar between two groups. Target heart rate was acheived in both dippers and non-dippers. CI was lower than normal in both groups. Dippers had higher HRR values than non-dippers (Table 3). HRR was positively correlated with the percentage decline of systolic and diastolic BP from day to night (r=0.255 p<0.001 and r=0.228 p=0.001, respectively). There were no correlation between CI and percentage of systolic and diastolic BP reduction from day to night (r=0.067 p>0.05 and r=0.16 p>0.05, respectively).

**TABLE 1:** Clinical characteristics of the patients.

| | Non-dippers (n=120) | Dippers (n=94) | p value |
|---|---|---|---|
| Age (years) | 55.2±11.4 | 54.7±11.0 | NS |
| Male (%) | 59 (49.2%) | 46 (48.9%) | NS |
| Female (%) | 61 (50.8%) | 48 (51.1%) | NS |
| Current smoker (%) | 21 (17.5%) | 16 (17%) | NS |
| Ejection fraction (%) | 59.1±4.5 | 60.0±4.8 | NS |
| Hyperlipidemia (%) | 22 (18.3%) | 17 (18.1%) | NS |
| Diabetes mellitus (%) | 18(15%) | 14(14.9%) | NS |
| Stroke (%) | 0 | 0 | NS |
| Coronary artey disease (%) | 11 (9.2%) | 9 (9.6%) | NS |
| **Medical treatment** | | | |
| ARB (%) | 50 (41.6%) | 41 (43.6%) | NS |
| ACE-I (%) | 35 (29.2%) | 27 (28.7%) | NS |
| Diuretic (%) | 5 (4.2%) | 4 (4.3%) | NS |

ACE I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; NS: Not significant.

**TABLE 2:** Systolic and diastolic BP of the patients during day and night.

| | Non-dippers mean±SD | Dippers mean±SD | p value |
|---|---|---|---|
| Day systolic BP (mmHg) | 134.3±14.1 | 134.0±10.8 | NS |
| Day diastolic BP (mmHg) | 84.4±10,5 | 84.9±8.3 | NS |
| Night systolic BP (mmHg) | 126.3±15.0 | 114.1±11.4 | <0.001 |
| Night diastolic BP (mmHg) | 79.9±9.8 | 72.3±7.3 | <0.001 |
| Systolic BP reduction (%) | 3.5±2.4 | 12.8±2.4 | <0.001 |
| Diastolic BP reduction (%) | 5.2±2.9 | 14.7±3.4 | <0.001 |

BP: Blood pressure; NS: Not significant.

**TABLE 3:** Exercise stress test values of the patients

| | Non-dippers | Dippers | p value |
|---|---|---|---|
| Resting HR | 82.5±12.8 | 79.2±12.1 | NS |
| Maximal HR | 145.4±14.2 | 147.2±13.3 | NS |
| Exercise capacity (METS) | 8.1±1,8 | 8.2±2.0 | NS |
| Duration of exercise (min) | 6.1±1.8 | 6.1±1.7 | NS |
| Target heart rate (%) | 87.3±10.7 | 88.1±10.8 | NS |
| Maximal systolic BP | 165±23 | 162±22 | NS |
| Maximal diastolic BP | 90.1±8.5 | 89.3±8.8 | NS |
| CI | 0.78±0.1 | 0.79±0.1 | NS |
| HRR | 29.1±4.6 | 31.8±4.6 | <0.001 |

BP: Blood pressure; CI: Chronotropic Index; HR: Heart rate; HRR: Heart rate recovery; NS: Not significant.

## DISCUSSION

Alterations in neural regulatory activity suggested as a cause of essential hypertension. Previous studies have adressed this problem by measuring the plasma catecholamine levels as an index of sympathetic tone and found that plasma noradrenaline levels were elevated in young patients with established hypertension.[14] In the earlier stages, arterial hypertension may be accompanied by sympathetic overactivity, decreased parasympathetic tone, and impaired activitiy of baroceptors leading tol blunted HRV.[15] Autonomic nervous system also plays a pivotal role in diurnal change of BP. Physiologically, BP has circadian rhythm. Normally,

heart rate, cardiac output, peripheral resistance and circulating catecholamines are reduced during sleeping. Autonomic dysfunction including abnormal circadian variation contributes to the non-dipper phenomenon. In non-dipper hypertensive patients physiological circadian fluctiation of autonomic functions decreased.[16] Nighttime norepinephrine and epinephrine excretion rates not reduced in non-dippers compared to dippers.[3] Hypertensive patients who had the most severe form of non-dipping had the highest level of morning sympathetic activity.[17] Vaile et al. reported that baroreflex sensitivity did not differ between dipper and non-dipper hypertensive patients but by sequence analysis technique they found that non-dipper patients had reduced sequences reflecting impairment of parasympathetic activity.[18] It has been suggested that impaired cardiovascular reflexes may contribute to the altered sympathovagal balance in non-dipper type hypertension.[19] Non-dipping pattern is associated with more severe target organ damage and mortality.[20]

CI and HRR are two commonly used techniques which reflect autonomic nervous system activity. During graded exercise heart rate increases as a result of sympathetic stimulation and vagal withdrawal. After exercise vagal tonus restored and heart rate returns its normal level. An attenuated HRR, reflects reduced parasympathetic nervous system activity.[21,22] Kannankeril et al. demonstrated that sympathetic withdrawal also contributes to early HRR.[23] Both attenuated response to exercise and slowed recovery of heart rate after exercise have prognostic value. In a study performed by Sandvik et al. resting HR and maximal exercise-induced HR measured in 1960 healthy men and followed 16 years. They found that difference between two heart rates and maximal exercise-induced HR predicted cardiovascular mortality.[9] HRR was a predictor of mortality in subjects with no history of congestive heart failure or ischemic heart disease and independently predicts mortality in patients with coronary artery disease.[3,10] HRR provides additional prognostic information in patients with heart failure undergoing cardiopulmonary exercise testing.[21]

In this representive study, we have demonstrated that HRR was significantly lower in non-dipper patients. We found that HRR was positively correlated with the percentage decline of systolic and diastolic BP from day to night. Our findings was consistent with the findings of Okutucu et al. They found that blunting of the nocturnal fall in BP was associated with a delayed recovery of heart rate after graded maximal exercide in both normotensive and hypertensive groups.[24] Another study performed with patients with mild to moderate hypertension showed that patients with lowest quintile for % night SBP fall had lower 1 min % HRR.[25] Impaired parasympathetic activity may result in decrease of HRR and loss of nocturnal BP dipping. In addition, we also showed that that chronotropic index was lower than normal in both dipper and non-dipper patients. Hypertensive patients has sympathetic overactivity and this phenomenon have a role both in intitiation and maintenence of hypertension.[26] Increased sympathetic activity at rest and decreased reactivity to exercise may contribute to the chronotropic incompetence in hypertensive patients. This increased sympathetic activity may result in failure of the sinus node -already oversaturated with sympathetic impulses- to maintain a modulation of heart rate and desensitization of cardiac receptors and abnormal heart rate response to exercise.[27,28]

Increased sympathetic activity increases cardiovascular workload and hemodynamic stress causes endothelial dysfunction, coronary artery spasm, left ventricular hypertrophy, serious arrhythmias, stroke, and mortality. In contrast, increased vagal activity exerts protective effect against ischemia related dysrhythmias and also reduces heart rate and blood pressure.[7] Increased cardiovascular mortality seen in non-dipper hypertensive patients may be the result of abnormalities of the autonomic nervous system activity.

In our study all of the patients were under antihypertensive treatment. β-blockers and calcium channel blockerse were stopped 48 hours before exercise testing. Therefore, medications were not influence HRR.

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