

## The effect of nondipper blood pressure pattern on target organ damage in patients with metabolic syndrome

Metabolik sendromlu hastalarda nondipper kan basıncı seyrinin hedef organ hasarı üzerine etkisi

Ahmet Soylu, M.D., Hakan Gulec, M.D., Yusuf Izzetin Alihanoglu, M.D., Osman Sonmez, M.D., Selim Suzi Ayhan, M.D., Hasan Gok, M.D.

Selcuk University, Faculty of Medicine, Department of Cardiology, Meram, Konya, Turkey

**Amaç:** Hem metabolik sendromun (MetS) hem de nondipper durumun (gece kan basıncı düşüşündeki yetersizlik) hedef organ hasarı ile ilişkili olduğu gösterilmiştir. Bu çalışmada MetS'li kişilerde nondipper durumun hedef organ hasarına etkisi araştırıldı.

**Çalışma planı:** Metabolik sendrom tanısı konan 82 hasta, 24 saatlik ambulatuvar kan basıncı izleme sonuçlarına göre dipper (n=35, 19 kadın, 16 erkek; ort. yaş 48.4±6.4) ve nondipper (n=47, 35 kadın, 12 erkek; ort. yaş 50.4±4.7) olarak iki gruba ayrıldı. Tüm çalışma grubunda kardiyak hasar konvansiyonel ve doku Doppler ekokardiyografi ile, böbrek hasarı ise 24 saatlik idrarda albümin atılımı ile değerlendirildi.

**Bulgular:** İki grup, yaş, beden kütle indeksi, diyabet varlığı, klinik ve 24 saatlik kan basıncı, gece ve gündüz kan basıncı değerleri, plazma lipit düzeyleri, sigara kullanımı, MetS ölçütlerinin dağılımı ve toplam MetS ölçütü sayısı bakımından benzer özellikteydi. Sol ventrikül tepe diyastolik erken miyokardiyal hız (Em)/tepe diyastolik gec miyokardiyal hız (Am) oranı nondipper grupta anlamlı derecede daha düşük bulundu (p=0.016). Sol ventrikül kütle indeksi, miyokart performans indeksi ve 24 saatlik idrar albümin atılımı nondipper grupta daha yüksek olmakla birlikte, fark anlamlı değildi (sırasıyla p=0.110, p=0.099 ve p=0.093). Çokdeğişkenli regresyon analizi sonucunda yaş artışı ve nondipper durumun bağımsız olarak Em/Am oranında azalmaya neden olduğu görüldü (sırasıyla;  $\beta=-0.25$ , p=0.020 ve  $\beta=-0.22$ , p=0.042).

**Sonuç:** Metabolik sendromlu kişilerdeki nondipper durumu diğer MetS bileşenlerinden bağımsız olarak hem kardiyak hem de böbrek hasarı ile ilişkili olabilir. Nondipper gruptaki diyastolik disfonksiyonun albüminüri düzeyindeki artıştan daha belirgin olması, bu kişilerde kardiyak hasarın böbrek hasarından daha ön planda olabileceğini düşündürmektedir.

**Anahtar sözcükler:** Albüminüri; kan basıncı izleme, ambulatuvar; ekokardiyografi, Doppler; metabolik sendrom X; ventrikül disfonksiyonu, sol/etiyojü.

**Objectives:** Both metabolic syndrome (MetS) and nondipping status (insufficient reduction in nocturnal blood pressure) have been linked with target organ damage. We evaluated the effect of nondipping status on target organ damage in subjects with MetS.

**Study design:** Eighty-two patients diagnosed as having MetS were divided into two groups according to the findings of 24-hour ambulatory blood pressure monitoring as dipper (n=35, 19 women, 16 men; mean age 48.4±6.4 years) and nondipper (n=47, 35 women, 12 men; mean age 50.4±4.7 years). Cardiac damage was assessed by conventional and tissue Doppler echocardiography, and renal damage by 24-hour urinary albumin excretion.

**Results:** The two groups were similar with regard to age, body mass index, presence of diabetes, smoking, clinical and 24-hour, daytime and nighttime blood pressures, plasma lipid profile, distribution of and the mean total number of MetS criteria. The ratio of early (Em) to late (Am) left ventricular peak diastolic myocardial velocities (Em/Am) was significantly lower in nondippers (p=0.016). Nondippers also had higher values of left ventricular mass index, myocardial performance index, and 24-hour urinary albumin excretion, but these differences did not reach a significant level (p=0.110, p=0.099, p=0.093, respectively). Multivariate regression analysis showed increasing age and nondipping status as independent factors associated with decreased Em/Am ratio ( $\beta=-0.25$ , p=0.020 and  $\beta=-0.22$ , p=0.042, respectively).

**Conclusion:** In subjects with MetS, nondipping status may be associated with both cardiac and renal damage independent of other components of MetS. Since the degree of diastolic dysfunction is more marked than that of albuminuria in nondippers, it may be extrapolated that the extent of cardiac damage surpasses renal damage in these subjects.

**Key words:** Albuminuria; blood pressure monitoring, ambulatory; echocardiography, Doppler; metabolic syndrome X; ventricular dysfunction, left/etiology.

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Corresponding address: Dr. Ahmet Soylu, Selçuk Üniversitesi, Meram Tıp Fakültesi, Kardiyoloji Anabilim Dalı, 42080 Konya. Tel: +90 332 223 63 67, e-mail:asoylu44@gmail.com

Metabolic syndrome (MetS) which is basically characterized by a cluster of obesity, increased blood pressure, components of impaired glucose and lipid metabolism is a major and common public health problem increasing cardiovascular morbidity and mortality. Cardiovascular target organ damage is mostly seen in patients with MetS, with a more rapid prognosis.<sup>[1]</sup> Several studies have shown concentric remodeling of the left ventricle, left ventricular hypertrophy, left ventricular diastolic dysfunction, dilation of the cardiac chambers and aorta, and increased urinary albumin excretion in patients with MetS.<sup>[2,3]</sup> Increased blood pressure alone, a major component of metabolic syndrome, leads to the development of cardiovascular target organ damage. Several 24-hour ambulatory blood pressure monitoring (ABPM) studies have demonstrated that severe target organ damage developed more in patients with insufficient reduction in nocturnal blood pressure (nondipper blood pressure).<sup>[4,5]</sup> There is a limited number of study investigating the relationship between MetS and nondipping status which has been shown to cause target organ damage even in normotensives.<sup>[5,6]</sup> In this study we investigated the effect of nondipping status on target organ damage in patients with MetS.

## PATIENTS and METHODS

A total of 82 patients with MetS<sup>[7]</sup> who visited the Cardiology Clinic and who satisfied the required criteria were included in the study. Patients with type 1 diabetes mellitus (DM), type 2 diabetes mellitus of more than three years or uncontrolled diabetes (fasting plasma glucose of >200 mg/dL), secondary hypertension (HT), renal failure, hepatic failure and/or major cardiac diseases (heart failure, coronary artery disease, arrhythmia, cardiac valvular disease), and those receiving antihypertensives were excluded from the study. All patients were informed about the study, and both verbal and written informed consents were obtained for voluntary participation.

During the baseline examination, weight, height, waist circumference, and hip circumference were measured by one examiner using the ambulatory standard measurement devices, during fasting and while the patient was standing. Waist circumference was considered as the narrowest diameter between the costal margin and the anterior superior iliac spine, while hip circumference was considered as the largest diameter over the gluteus maximus posteriorly and symphysis pubis anteriorly. Body mass index (BMI) was calculated using the formula "weight (kg)/height (m<sup>2</sup>)", while body surface area (m<sup>2</sup>) was calculated using the formula, "0.007184 x weight (kg)0.425 x height (cm)0.725.

Clinical blood pressure (BP) measurements were performed using a mercury sphygmomanometer following 10 minutes rest in the sitting position. Three consecutive readings were obtained using 2-minutes interval settings and the mean of these readings were considered as clinical BP.

A 24-hour ABPM was performed using a portable digital recorder (Reynolds Medical's Tracker NIBP2, Del Mar Reynolds Medical, Hertford, UK). The recorder was programmed to function between 07 AM-11PM (daytime BP values) for every 20 minutes and between 11PM-07 AM for every 30 minutes (nocturnal BP values). Patients with mean circadian systolic BP of >130 mmHg and/or diastolic BP of >80 mmHg were considered to be hypertensive.<sup>[8]</sup> The percentage of nocturnal blood pressure decline was calculated using the following formula: nocturnal BP decline (%) = (Daytime BP-Nocturnal BP) x 100 / Daytime BP. Patients were divided into two groups according to the decline in systolic and diastolic blood pressures as dipper ( $\geq 10\%$ ; n=35, 19 women, 16 men; mean age 48.4 $\pm$ 6.4 years) and nondipper (<10%; n=47, 35 women, 12 men; mean age 50.4 $\pm$ 4.7 years).

After an overnight fasting period of 8 hours, venous blood samples were drawn and analyzed for plasma glucose level, urea, creatinine, total cholesterol level, triglycerides, high density lipoprotein (HDL) cholesterol level, and low density lipoprotein (LDL) cholesterol level. A 24-hour urine sample was also collected for albumin and creatinine clearance analysis.

**Echocardiographic evaluation.** Echocardiography was performed by a cardiologist who was blinded for the other patient data using a Philips HD11 echocardiography device and 2-4 MHz phased-array transducer in accordance with the American Society of Echocardiography Guidelines.<sup>[9]</sup> The M-mode probe was perpendicularly positioned in the long axis of the left ventricle (LV), in front of the mitral valve tips from the parasternal long axis view. LV diastolic inner diameter (LVDD) and LV systolic inner diameter (LVSD), and LV diastolic interventricular septal wall thickness (IVS) and posterior wall thickness (PWT) were measured. Left ventricular mass was calculated using the 1.04[IVS+LVDD+PWT]<sup>3</sup>-(LVDD)<sup>3</sup>-13.6 formula, while the relative wall thickness was calculated using the 2xPWT/LVDD formula.<sup>[10,11]</sup> Left ventricular mass index (LVMI) was calculated by dividing individual left ventricular mass into body surface area. Two dimensional echocardiography with apical four chamber view was performed to measure left ventricular ejection fraction using modified Simpson's method.<sup>[12]</sup>

**Table 1. Demographic, clinical, and laboratory characteristics of the patient groups**

	Dipper (n=35)			Nondipper (n=47)			p
	n	%	Mean±SD	n	%	Mean±SD	
Age			48.4±6.4			50.4±4.7	0.11
Sex							0.06
Female	19	54.3		35	74.5		
Male	16	45.7		12	25.5		
Body mass index (kg/m <sup>2</sup> )			31.5±3.3			32.0±3.6	0.50
Waist circumference (cm)			102.5±7.0			102.9±7.5	0.82
Hypertension	12	34.3		19	40.4		0.60
Type 2 diabetes mellitus	10	28.6		15	31.9		0.75
Dyslipidemia	10	28.6		9	19.2		0.32
Cigarette smoking	6	17.1		12	25.5		0.36
Laboratory findings							
Total cholesterol (mg/dL)			207.6±35.9			200.7±30.8	0.35
Fasting blood glucose (median) (mg/dL)			104			107	0.33
Interquartile intervals 25-75			92±119			99±117	
HDL-C (mg/dL)			42.3±8.2			45.2±9.7	0.15
LDL-C (mg/dL)			130.6±29.9			124.1±27.6	0.31
Triglycerides			168.0±77.0			171.8±84.0	0.83
Blood pressure (mmHg)							
Clinical							
Systolic			132.2±16.3			136.0±19.5	0.354
Diastolic			83.6±10.0			84.5±13.7	0.74
Circadian							
Systolic			123.0±13.2			124.1±10.2	0.67
Diastolic			75.4±8.2			76.5±7.8	0.50
Daytime							
Systolic			129.4±13.7			126.7±10.9	0.32
Diastolic			80.5±9.3			78.8±8.2	0.38
Nocturnal							
Systolic			110.6±12.1			119.1±9.8	<0.01
Diastolic			65.6±7.5			72.2±7.5	<0.01

Mitral flow velocity was measured using pulsed wave Doppler echocardiography with apical four chamber view, positioning the probe in the coaptation points of the valves during diastole. Peak early diastolic flow velocity (E), peak late diastolic flow velocity (A), E/A ratio, and the E wave deceleration time (EDT) were calculated.

The peak systolic myocardial (Sm), peak early diastolic myocardial (Em), and peak late diastolic myocardial (Am) tissue velocities, isovolumetric relaxation time (IVRT), isovolumetric contraction time (IVCT) and ejection time (ET) were measured from the septum and left ventricular lateral wall mitral annulus, by the tissue Doppler method. Mean left ventricular values were obtained using the arithmetic mean of each parameter derived from septal and lateral walls. In addition, the mean LV myocardial performance index (MPI) was calculated using these mean values and the (IVRT+IVCT)/ET formula. Doppler examinations were based on the arithmetic mean of three consecutive measurements.

**Statistical analysis.** All data were expressed in

mean±standard deviation (SD), median (interquartile percentage intervals of 25 and 75) or number or percentage. The t-test or Mann-Whitney U test were used to compare groups and independent samples, while Chi-square test was used to compare categorical variables. The relationship between dependent variables was established by correlation analysis. Multivariate retrospective linear regression analysis was also performed to evaluate parameters which were considered to likely have an effect on target organ damage. A p value of <0.05 was regarded as statistically significant. Statistical analyses were performed using SPSS 13.0 program.

## RESULTS

Demographic characteristics of patient groups are shown in Table 1. There was no significant difference between the groups in terms of age, BMI, presence of DM, clinical and circadian blood pressure, daytime and nocturnal blood pressure values, plasma lipid levels, and cigarette smoking. As anticipated, nocturnal systolic and diastolic blood pressure values were higher in nondippers.

**Table 2. Comparison of MetS criteria between the groups**

Metabolic Syndrome Criteria	Dipper (n=35)		Nondipper (n=47)		p
	n	%	n	%	
Triglyceride	18	51.4	26	55.3	0.73
HDL-C	23	65.7	26	55.3	0.34
Blood pressure	17	48.6	28	59.6	0.32
Fasting blood glucose	22	62.9	37	78.7	0.11
Mean number of criteria excluding waist circumference	2.29±0.46		2.49±0.72		0.15

The MetS criteria distribution excluding waist circumference are summarized in Table 2. No significant difference was found between the groups in terms of distribution of MetS criteria and the mean total number of criteria.

Echocardiographic findings of both groups are given in Table 3. The LV mean Em/Am ratio was found to be significantly lower in the nondipper group compared to dipper group ( $p=0.016$ ). Although there was no significant difference between the groups in respect of the other echocardiographic parameters, nondippers had higher values of LVMI and MPI compared to dippers ( $p=0.110$  and  $p=0.099$ , respectively).

A multivariate linear regression analysis was performed to evaluate factors, which were considered to likely influence Em/Am ratio including age, sex, BMI, HT, DM, number of MetS criteria, dipper-nondipper status, clinical, circadian, daytime and nocturnal systolic and diastolic blood pressures. Increasing age and nondipper status were found to result in decreased Em/Am ratio

( $\beta=-0.25$ ,  $p=0.020$  and  $\beta=-0.22$ ,  $p=0.042$ , respectively) independent of the other factors. The effect of age on Em/Am ratio was more significant compared to nondipper status.

Nondippers also had higher values of urinary albumin excretion as assessed by 24-hour urinary albumin excretion during evaluation of renal function; however, this difference did not reach a statistically significant level ( $p=0.093$ ). On the other hand, there was no significant difference between the groups regarding the other renal function parameters (Table 4).

## DISCUSSION

In this study investigating the effect of nondipper blood pressure on target organ damage in patients with MetS, diastolic dysfunction was found to be more evident in nondippers. In addition, nondippers had higher value of LVMI, MPI, and 24-hour urinary albumin excretion compared to dippers. However, this difference was not statistically significant.

**Table 3. Comparison of echocardiographic findings between the patient groups**

	Dipper (n=35)	Nondipper (n=47)	p
Ejection fraction (%)	64.4±1.6	64.3±2.2	0.881
Left ventricular mass (g)	180.3±47.1	193.8±60.3	0.276
Left ventricular mass index (g/m <sup>2</sup> )	93.2±20.3	102.5±29.1	0.110
Relative wall thickness	0.43±0.07	0.42±0.07	0.393
Diastolic transmitral flow velocity (cm/sec)			
Early velocity (E)	73.6±19.4	0.6±18.7	0.485
Late velocity (A)	82.2±19.0	5.3±17.9	0.457
E/A	0.9±0.2	0.8±0.2	0.190
E wave deceleration time (msec)	159.0±31.4	162.8±40.6	0.641
Peak myocardial velocities (cm/sec)			
Systolic velocity	8.7±1.4	8.3±1.3	0.173
Diastolic velocity			
Early diastolic velocity (Em)	8.9±2.1	8.2±2.2	0.115
Late diastolic velocity (Am)	10.9±2.1	11.5±1.9	0.186
Em/Am	0.8±0.2	0.7±0.2	0.016
E/Em	8.7±2.7	9.0±3.1	0.664
Isovolumetric relaxation time (msec)	79.6±13.5	84.9±15.0	0.103
Isovolumetric contraction time (msec)	70.0±12.7	74.3±15.5	0.177
Ejection time (msec)	269.8±22.0	269.6±29.7	0.974
Myocardial performance index	0.55±0.08	0.59±0.12	0.099

**Table 4. Comparison of renal functions between the groups**

	Dipper (n=35)	Nondipper (n=47)	p
Urea (mg/dL)	23.5±5.8	26.2±8.32	0.106
Plasma creatinine (mg/dL)	0.82±0.15	0.84±0.17	0.518
Creatinine clearance (mg/dL)	116.5±30.4	106.9±27.8	0.140
Urinary albumin excretion (median) (mg/24 hours)	16.8	27.6	0.093
Interquartile intervals 25-75	10.0±40.5	12.3±84.0	

The risk for development of cardiovascular disease is known to be higher in individuals with MetS.<sup>[1]</sup> Several studies evaluating target organ damage have shown that there is a relationship of MetS with increased left ventricular mass and increased urinary albumin excretion.<sup>[1,13]</sup> Given the fact that both increased left ventricular mass and urinary albumin excretion increase the risk of cardiovascular disease (CVD),<sup>[14,15]</sup> it is critical to investigate the presence of target organ damage in these patients to perform a more accurate risk evaluation.

Blood pressure values obtained by ambulatory blood pressure monitoring was shown to be more associated with target organ damage than clinical BP measurements.<sup>[16,17]</sup> Daily BP rhythm can also be evaluated and certain cardiovascular abnormalities shown to be related to poor prognosis can be detected using ABPM.<sup>[18]</sup> Many studies have demonstrated that nondipping status, one of the major abnormalities of daily BP rhythm, is associated with target organ damage in both hypertensives and normotensives.<sup>[5,6,19]</sup> Although several studies have evaluated the presence and extent of hypertension in patients with MetS by ABPM, the relationship between nondipping status and target organ damage has not been thoroughly investigated.<sup>[3,20]</sup>

Tissue Doppler imaging technique is known to give more early and accurate results regarding diastolic dysfunction, compared to conventional Doppler.<sup>[21]</sup> Although no significant difference was observed between the groups in respect of conventional Doppler parameters, nondippers were shown to have a significantly lower Em/Am ratio as demonstrated by tissue Doppler. This finding suggests a more severe LV diastolic dysfunction in nondippers with MetS. On the other hand, nondippers were shown to have higher scores of MPI which provides information on global (systolic and diastolic) myocardial functions (p=0.009) with a value close to statistical significance.<sup>[22]</sup> Although no significant difference was obtained between the groups in terms of parameters (IVRT, IVCT, and ET) which were used to calculate MPI, demonstration of the largest increase in IVRT (Table 3) suggests that this partial increase in MPI is mostly due to diastolic dysfunction. Nondippers have also been shown to have a higher but not statistically significant value of

LVMI in this study. Based on the adverse effect of diastolic dysfunction and increased left ventricular mass on cardiovascular events,<sup>[14,23]</sup> results of this study may explain the underlying mechanism of the increased risk for development of cardiovascular disease in patients with MetS.

Assessment of renal damage demonstrated a tendency for increased 24-hour urinary albumin excretion in nondippers. Increased urinary albumin excretion is known to be an early finding of renal damage<sup>[24,25]</sup> and even small increases to the level of albuminuria are known to increase the risk of CVD.<sup>[15]</sup> As a result, increased urinary albumin excretion in nondippers with MetS may indicate not only a severe renal damage, but also increased CVD risk.

Studies investigating the relationship between MetS and nondipper blood pressure have shown that the probability of nondipper status increases as the number of MetS criteria increases.<sup>[20]</sup> Therefore, target organ damage may be associated with both the number of MetS criteria<sup>[26]</sup> and as a result increased likelihood of nondipping status in patients with MetS. In our study there was no difference between dippers and nondippers in respect of the distribution MetS criteria (Table 2). Multivariate analysis also showed that the number of MetS criteria had no significant effect on Em/Am ratio. These findings suggest that the relationship of target organ damage with nondipping status is not significantly associated with the number of MetS criteria.

Although the underlying mechanisms leading to target organ damage in nondippers with MetS is still unknown, the role of mechanisms which causes nondipping status in circadian BP rhythm is being taken into consideration. Review of the literature shows that increased sympathetic nervous system activation and renin-angiotensin-aldosterone system play a role in the pathophysiology of nondipper blood pressure.<sup>[27,28]</sup> Angiotensin II is known to lead to some adverse cardiovascular effects. Among these are cardiomyocyte hypertrophy, programmed cell death, myocardial fibrosis, endothelial dysfunction, and vasoconstriction.<sup>[29]</sup> On the other hand, high level of aldosterone may also lead to increased extracellular matrix and collagen via myocardial mineralocorticoids receptors

independent of increased blood pressure, and thereby leading to cardiac hypertrophy.<sup>[30]</sup> As a result, both angiotensin II and aldosterone may increase LV mass and diastolic dysfunction, by increasing myocardial fibrosis and amount of collagen.<sup>[31,32]</sup>

In conclusion, nondipping status may be associated with both cardiac and renal damage independently from increased blood pressure and the other components of MetS. Moreover, the greater significance of increased diastolic dysfunction to the level of albuminuria in nondippers suggests that cardiac damage may be more severe than renal damage.

**Limitations of the study.** The small sample size is the major limiting factor in this study followed by unrepeatable ABPM. Also, it would have been more appropriate to measure daytime and nocturnal BP according to reports by the patients about when they went to bed and when they woke-up, but not based on a certain predefined time period. Tissue Doppler examination based on septal and lateral walls and not on all four walls of the LV is another echocardiographic drawback in the study.

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