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ORIGINAL ARTICLE

Extreme Nocturnal Blood Pressure Dipping is Associated With Increased Arterial Stiffness in Individuals With Components of the Metabolic Syndrome

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Background and Purposes: The metabolic syndrome (MS) and abnormal nocturnal blood pressure (BP) dipping are both associated with increased risk of cardiovascular events. An association between MS and arterial stiffness was reported. This study aimed to examine the relationship between arterial stiffness as determined by the Cardio-Ankle Vascular Index (CAVI) and the nocturnal BP dipping pattern in normotensive individuals with one or more risk components of MS.

Methods and Results: A total of 73 normotensive individuals who met at least one of the five National Cholesterol Education Program Adult Treatment Panel III criteria were included. The MS score was calculated according to the GISSI Study. Ambulatory BP was recorded every 30 minutes for a 48-hour period. Individuals with MS and those without MS did not significantly differ in CAVI ($p = 0.040$) or nocturnal systolic blood pressure (SBP) dipping ($p = 0.909$). Controlling for age, CAVI was not significantly correlated with the MS score ($p = 0.067$). CAVI significantly correlated with the magnitude ($\rho = 0.29$, $p = 0.014$) and the percentage ($\rho = 0.29$, $p = 0.013$) of nocturnal SBP dipping. CAVI independently predicted the magnitude of nocturnal SBP reduction ($\beta = 0.364$, $p = 0.002$) even after adjusting for age and nighttime SBP. The extreme dippers had significantly higher CAVI values than the nondippers ($p = 0.012$) and a trend toward higher CAVI than the dippers ($p = 0.031$).

Conclusion: MS is associated with neither arterial stiffness nor nocturnal dipping pattern in normotensives. However, in normotensive individuals with risk components of the MS, arterial stiffness is related to an extreme dipping pattern.

1. Introduction

A cluster of cardiovascular and metabolic risk factors, the metabolic syndrome (MS), is associated with increased risk of cardiovascular morbidity and mortality.[1] Carotid-femoral pulse wave velocity (PWV), a widely used noninvasive index of central arterial stiffness, is a predictor of all-cause and cardiovascular mortality[2] as well as fatal stroke[3] in hypertensive populations. MS is associated with increased arterial stiffness (i.e., increased PWV),[4,5] which may accelerate the development of adverse cerebral and cardiac events. Recently, a new measure of arterial stiffness independent of blood pressure (BP) changes, the Cardio-Ankle Vascular Index (CAVI), has been developed.[6] Increased CAVI in diabetics compared with that in nondiabetics was reported.[7] CAVI has also been shown to be associated with left ventricular diastolic dysfunction,[8] coronary atherosclerosis,[9] and carotid arteriosclerosis indexed by carotid artery intima-media thickness.[7] Moreover, an association between MS and CAVI was reported.[10]

An abnormal nocturnal variation pattern of BP [e.g., decreased nocturnal BP fall (nondipping), extreme dipping pattern, or elevated nocturnal BP (reverse dipping pattern)] has been demonstrated to be associated with higher incidences of cardiovascular events and is an independent predictor of future cerebrovascular events.[11–13] It is thus likely that individuals with MS may have abnormal patterns of nocturnal BP variation. However, previous data on the question of whether MS is associated with

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decreased nocturnal BP fall remains conflicting.[14–16] An abnormal nocturnal BP variation pattern has been suggested to be related to increased arterial stiffness in untreated patients with essential hypertension[17] or with resistant hypertension.[18] It is possible that the relationship between MS and abnormal patterns of nocturnal BP variation depends on the degree of arterial stiffness. It is thus of interest to study the association between arterial stiffness and nocturnal BP variation in individuals with one or more components of MS. This study aimed to examine the relationship between CAVI and abnormal patterns of nocturnal BP variation in normotensive individuals with one or more risk components of MS.

2. Methods

2.1. Participants

Participants were recruited from a Health Check-up Center or referred by an endocrinologist from the Department of Metabolism and Endocrinology of a hospital located in northern Taiwan. All participants gave informed consent. The experimental protocols and the process for obtaining informed consent were approved by the Institutional Review Board of the study hospital.

In this study, MS was defined according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III criteria with modified cutoffs for waist circumference for use in Asians[19] as follows: (1) abdominal obesity (i.e., waist circumference >90 cm in men and >80 cm in women); (2) hypertriglyceridemia (i.e., >150 mg/dL or on drug treatment for elevated triglycerides); (3) low high-density lipoprotein cholesterol (HDL-C) (i.e., <40 mg/dL in men and <50 mg/dL in women or on drug treatment for low HDL-C); (4) high BP (i.e., ≥130/≥85 mmHg); and (5) high fasting glucose (i.e., ≥110 mg/dL or on drug treatment for elevated blood sugar). Participants were eligible if (1) their clinic BP values were less than 140 mmHg systolic and less than 90 mmHg diastolic; (2) they had never been treated with antihypertensive medication; (3) they had at least one of the five NCEP ATP III components that defined MS; and (4) they were free from congestive heart failure, previous myocardial infarction, cardiac valve disease, history of coronary disease, known vasovagal dysfunction, atrial fibrillation, and other major dysrhythmias.

On the basis of our inclusion criteria, all participants had a systolic BP (SBP) less than 140 mmHg and a diastolic BP less than 90 mmHg. Participants who had any three or more of the five components based on the NCEP ATP III MS definition were defined as individuals with MS.

2.2. Measurements

2.2.1. Ambulatory BP

In cooperation with the participant, ambulatory BP monitoring was scheduled on days that represented the participant's typical day of the week, during which he or she was to keep a regular sleep-and-wake pattern. Participants were discouraged to wear the monitor during off-work/school days or days with special life events. No shift workers were included in this study. The monitor (SpaceLabs 90217; SpaceLabs Health Care, Issaquah, WA, USA) was programmed to take BP measurements every 30 minutes for a consecutive 48-hour period.

Because categorization of dipping patterns based on a single 24-hour ambulatory BP measurement is only moderately reproducible, the mean ambulatory BP measurements over 48 hours were used as suggested by a previous study.[20] Ambulatory BP recordings with at least 70% satisfactory readings out of the maximum number of possible readings (48 readings) per 24 hours on both days were included in the analysis.

2.2.2. Cardio-Ankle Vascular Index

CAVI was measured automatically by the VaSera device (VS-1000; Fukuda Denshi, Tokyo, Japan) from the measurement of BP and PWV, while monitoring of heart sounds and electrocardiogram. $CAVI = a\{(2\rho/\Delta P) \times \ln(Ps/Pd)PWV^2\} + b$, where Ps and Pd are SBP and diastolic BP, respectively; PWV is pulse wave velocity between the heart and ankle; ΔP is $Ps - Pd$; ρ is blood density; and a and b are constants.[6] Accordingly, CAVI is presented in numerals without units of measurement.

For the measurement of CAVI, the participant was placed in the supine position. Brachial pulse waves and ankle pulse waves were detected with two arm cuffs and two ankle cuffs. Electrocardiogram and heart sounds were monitored. The BP was measured at the brachial artery. Two CAVI measurements were taken after 5 minutes of rest. The average of the two CAVI values was used in the analysis.

2.2.3. Body weight, height, and waist circumference

Anthropometric data included body height in centimeters, weight in kilograms, body mass index (BMI) in kg/m^2, and waist circumference in centimeters. BMI was calculated using the formula: weight (kg)/height^2 (m^2). Waist circumference was measured at the midpoint between the bottom of the rib cage and above the top of the iliac crest from participants at minimal respirations.

2.2.4. Metabolic profile

Blood samples were drawn after the participants had been fasted for at least 8 hours. The blood samples were analyzed by a chemistry analyzer (UniCel DxC 800 Synchron Clinical System; Beckman Coulter, Inc., Brea, CA, USA) to determine the levels of blood triglycerides, HDL-C, and glucose.

2.2.5. Calculations

The MS score (i.e., GISSI score) was calculated. According to the GISSI Study, points were assigned for each risk factor, including male sex (3 points); age greater than 50 years (4 points); hypertension (2 points); BMI (0, 3, or 6 points); triglycerides (0, 5, 7, or 9 points); HDL-C (0, 3, or 5 points); fasting glucose level (0, 5, 10, 16, or 28 points).[21] The highest possible score for GISSI is 57 points, with a higher score indicating a greater risk of developing diabetes.

The day–night systolic BP (SBP) difference, or nocturnal SBP reduction, was calculated as the difference between the mean daytime (awake) pressure and the mean nighttime (asleep) pressure, using the individual boundaries between periods of sleep and wake time as indicated by each participant's diary. The percentage of dipping was calculated using the following formula: {(mean daytime SBP − mean nighttime SBP) ÷ mean daytime SBP} × 100%.

2.3. Dipper groups

Participants whose nighttime SBP was at least 10% lower than the mean daytime SBP were defined as dippers, whereas in nondippers, no reduction in nighttime SBP was noted or the reduction did not exceed 10% of the mean daytime SBP. Extreme dippers were defined as those with a 20% or greater nocturnal decline in SBP.

2.4. Statistical procedure

Data were presented as mean (standard deviation). Bivariate correlations of the GISSI score, CAVI, and nocturnal SBP reduction were examined with the Spearman correlation. Differences in CAVI and ambulatory BP (ABP) profiles between individuals with and without MS were tested by Student's unpaired *t* test. Differences in CAVI and metabolic profiles among dippers, nondippers, and extreme dippers were examined by the analysis of variance for

Table 1 Demographic and clinical characteristics of the study participants according to the metabolic syndrome status

Variables	Metabolic syndrome criteria*		p
	≥3 (n = 61)	<3 (n = 12)	
Age (yr)	47.89 (10.26)	48.08 (5.65)	0.925
Sex, n (%)			1.000
Male	44 (72.1)	9 (75.0)	
Female	17 (22.9)	3 (25.0)	
Blood pressure (mmHg)			
Systolic	127.97 (7.43)	119.33 (5.42)	<0.001
Diastolic	82.34 (5.71)	79.67 (6.96)	<0.001
Waist circumference (cm)	95.14 (7.87)	84.83 (7.11)	<0.001
Body mass index (kg/m^2)	27.46 (3.17)	24.15 (2.00)	0.001
Triglycerides (mg/dL)	207.25 (111.07)	229.42 (168.65)	0.566
High-density-lipoprotein cholesterol (mg/dL)	36.66 (6.22)	37.67 (7.20)	0.617
Fasting sugar (mg/dL)	141.26 (47.98)	121.00 (42.66)	0.178
Metabolic syndrome score	40.48 (7.69)	33.75 (10.61)	0.012
Cardio-Ankle Vascular Index	7.58 (1.12)	7.56 (0.99)	0.940
Dipping (mmHg)	17.89 (7.15)	18.15 (7.14)	0.909
Dipping (%)	14.07 (0.05)	15.85 (0.06)	0.280

Values are expressed in means (standard deviations) unless indicated otherwise.
* The metabolic syndrome criteria based on the National Cholesterol Education Program Adult Treatment Panel III.

continuous variables that were normally distributed, the χ^2 test for categorical variables, and the Kruskal–Wallis test for continuous variables that were not normally distributed. *Post hoc* comparisons between groups for the data examined by the analysis of variance were performed using the Tukey method. The Mann–Whitney *U* test with an adjusted significance level at 0.0167 (0.05/3) was used to test the pairwise group differences for the data examined by the Kruskal–Wallis test. Multiple regression analysis was performed to determine whether CAVI independently predicted the magnitude of nocturnal SBP reduction after adjusting for possible confounders.

3. Results

A total of 73 participants with a mean age of 46.9 ± 9.6 years were included in the study. Among them, 73% were males and 67% had diabetes mellitus. A comparison of the clinical characteristics between diabetics ($n = 49$) and nondiabetics ($n = 24$) showed that the two groups were not significantly different in clinic BP, ABP profiles, anthropometric measurements, metabolic profiles, and CAVI values (all $p > 0.05$), with the exception of fasting glucose levels ($p < 0.001$) and GISSI scores ($p = 0.001$). As expected, diabetics had higher fasting glucose levels (155.1 ± 49.2 *vs.* 102.9 ± 10.3) and higher GISSI scores (41.5 ± 8.4 *vs.* 34.9 ± 7.2).

Sixty-one participants had three or more NCEP ATP III components of MS, and 12 participants had less than three components. A comparison of the risk factors between individuals with MS and those without MS revealed that the two groups were significantly different in clinic BP measurements (both $p < 0.001$), waist circumference ($p < 0.001$), and BMI ($p = 0.001$), but not significantly different in age, sex, triglycerides, HDL-C, and fasting blood sugar (Table 1). As expected, the GISSI scores were significantly different between the groups ($p = 0.012$). However, the two groups were not significantly different in CAVI values ($p = 0.94$), the magnitude of nocturnal SBP reduction ($p = 0.909$), and the percentage of nocturnal SBP reduction ($p = 0.280$) (Table 1).

Examined by the Spearman correlation, CAVI values were significantly associated with age ($\rho = 0.34$, $p = 0.003$); the magnitude of nocturnal SBP reductions ($\rho = 0.29$, $p = 0.014$); the percentage of nocturnal SBP dipping ($\rho = 0.29$, $p = 0.013$); and the GISSI score ($\rho = 0.31$, $p = 0.007$). The GISSI score was not significantly associated with nocturnal SBP reduction in absolute values ($p = 0.388$) or the percentage of SBP dipping ($p = 0.787$). Partial correlation revealed that CAVI was not significantly related to the GISSI score ($p = 0.067$) after adjusting for age. Multiple regression analysis was performed with nocturnal SBP reduction as the dependent variable and age, nighttime SBP, and CAVI as the independent variables (Table 2). Data showed that CAVI ($\beta = 0.346$, $p = 0.002$) and nighttime SBP ($\beta = -0.223$, $p = 0.043$) were independent predictors of nocturnal SBP reduction but not age ($p = 0.354$). Together they explained 16% of the variance in nocturnal SBP reduction.

Most (65.8%) of the study sample was dippers. The prevalences of a nondipping pattern and an extreme dipping pattern were 16.4% and 17.8%, respectively. As can be seen in Table 3, the three groups with different dipping patterns did not significantly differ in age, sex, the proportion of diabetics, the GISSI score, or the components of MS with the exception of triglycerides ($p = 0.033$). *Post hoc* comparisons revealed that the extreme dippers had significantly higher levels of triglycerides than the nondippers ($p = 0.013$) and dippers ($p = 0.031$). In terms of the ABP profile, nondippers had a significantly higher nighttime SBP than dippers ($p = 0.001$) and extreme dippers ($p = 0.004$). Similarly, the Kruskal–Wallis test showed that the three dipper groups significantly differed in CAVI values ($p = 0.026$). *Post hoc* comparisons with an adjusted significance level at 0.0167 revealed that the CAVI value of the extreme dippers was significantly higher than that of the nondippers ($p = 0.012$) but not that of the dippers ($p = 0.031$) (Figure 1).

4. Discussion

It has been demonstrated that MS is associated with increased arterial stiffness.[4,5] Arterial stiffness has been reported to predict cerebrovascular and cardiovascular events.[2,3] In individuals with stiff central arteries, there is a decrease in diastolic pressure, resulting in increased left ventricular afterload and myocardial oxygen demand.[22] Arterial stiffness has thus been postulated to be a pathway through which MS leads to cardiovascular diseases.[23] The measurement of arterial stiffness is complicated by its dependence on BP. Recently, CAVI, a new noninvasive parameter of arterial stiffness that is independent of BP, has been developed.[6] Contradictory to previous studies in which CAVI values were higher in obese individuals with MS than in those without MS,[10] this study demonstrated that CAVI values were not significantly associated with the MS score (i.e., GISSI score) after controlling for age. Thus, in a group of normotensive individuals with components of MS, the effect of MS on arterial stiffness, if any, may be mainly attributed to the effect of age. These findings are in concert with the notion that the components of MS but not the status *per se* are associated with arterial stiffness suggested by Tentolouris et al.[24]

In this study sample, the prevalence of a nondipping BP pattern was around 16%. The prevalence of a nondipping BP pattern was reported to be higher in patients with MS than in those without MS.[25] In this study, we did not find an association between dipping and MS. We also found that individuals with different dipping patterns were not significantly different in the MS score or the

Table 2 Predictors of nocturnal systolic blood pressure reduction examined by multiple regression (adjusted $R^2 = 0.159$)

Variables	β	95% CI of β	p
Cardio-Ankle Vascular Index	0.346	0.839 to 3.643	0.002
Nighttime systolic blood pressure	−0.223	−0.303 to −0.005	0.043

CI = confidence interval.

Table 3 Comparison of the demographic and metabolic characteristics according to the dipping status

Variables	Dipping status			*p*
	Extreme dippers ($n = 13$)	Nondippers ($n = 12$)	Dippers ($n = 48$)	
Age	51.46 (7.87)	44.42 (8.25)	47.83 (10.16)	0.188*
Sex, *n* (%)				0.060†
Men	12 (92)	6 (50)	35 (73)	
Women	1 (8)	6 (50)	13 (27)	
Diabetes mellitus (yes), *n* (%)	9 (69)	5 (42)	35 (73)	0.118†
Body mass index (kg/m^2)	25.25 (1.64)	28.05 (3.66)	27.08 (3.34)	0.079*
Waist circumference (cm)	92.3 1(4.84)	92.92 (11.05)	93.88 (8.85)	0.824*
Triglycerides (mg/dL)	283.69 (184.09)§,‖	163.83 (77.22)	202.94 (101.81)	0.033*
High-density-liproprotein cholesterol (mg/dL)	36.23 (7.26)	37.50 (7.76)	36.81 (5.82)	0.885*
Fasting blood sugar (mg/dL)	134.54 (47.10)	117.50 (27.09)	143.96 (50.67)	0.218*
Blood pressure (mmHg)				
Systolic	124.15 (8.75)	128.17 (9.06)	126.79 (7.22)	0.415*
Diastolic	80.77 (6.02)	82.83 (5.37)	81.98 (6.16)	0.686*
Ambulatory blood pressure (mmHg)				
Daytime systolic	127.67 (12.39)	124.14 (10.65)	123.21 (10.64)	0.434*
Daytime diastolic	87.43 (10.48)	80.75 (9.46)	80.37 (7.16)	0.118*
Ambulatory blood pressure (mmHg)				
Nighttime systolic	99.92 (10.22)	115.60 (9.96)¶,#	105.59 (8.88)	<0.001*
Nighttime diastolic	68.08 (12.40)	73.73 (7.85)	68.07 (6.42)	0.053*
Metabolic syndrome score	37.92 (10.91)	36.42 (9.17)	40.50 (7.57)	0.349‡

Values are expressed in means (standard deviations) unless indicated otherwise.
* Group comparison by the analysis of variance; † Group comparison by the χ^2test; ‡ Group comparison by the Kruskal–Wallis test; § Extreme dippers > nondippers, $p = 0.013$; ‖ Extreme dippers > dippers, $p = 0.031$; ¶ Nondippers > extreme dippers, $p = 0.004$; # Nondippers > dippers, $p < 0.001$ (*post hoc* comparisons by the Tukey test).

components of MS, with the exception that the extreme dippers had significantly higher levels of triglycerides than dippers and nondippers. The observed discrepancy between our findings and previous findings was possibly because of the difference in the populations studied. In the present study, we only included individuals with normal BP, whereas in the previous study, untreated hypertensive patients were included.

A blunted decrease in nocturnal BP has been associated with increased arterial stiffness.[17,18] Surprisingly, we did not find a presumably negative association between the level of arterial stiffness and the magnitude of nocturnal dipping. Instead, the magnitude and the percentage of BP dipping increased as the level of arterial stiffness, as measured by CAVI, increased. Moreover, CAVI independently predicted the magnitude of BP dipping even after adjusting for age and nighttime BP. The positive association between arterial stiffness and the magnitude of nocturnal BP fall observed in the present study may mainly be attributed to the increased arterial stiffness in the extreme dippers. The cause of an increase in arterial stiffness in the extreme dipping status of nighttime BP is probably related to impaired baroreflex sensitivity. Sympathetic and parasympathetic systems play important roles in the short-term regulation of BP through baroreflex.[26] Baroreceptors respond very quickly to BP changes to maintain a stable BP. Increased arterial stiffness may diminish baroreflex sensitivity,[27] which in turn, causes vascular adrenergic hypersensitivity[28] and consequently orthostatic hypertension, coupled with reduced circulating blood volume leading to an extreme dipping status of nighttime BP.[29]

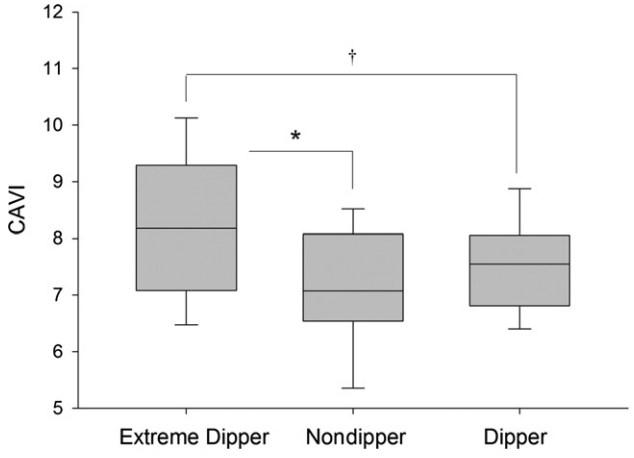

Figure 1 Box plot showing medium and dispersion of Cardio-Ankle Vascular Index (CAVI) distribution according to the dipping status. *$p = 0.012$; †$p = 0.031$ (not significant). Lines within boxes represent median values. Upper and lower boundaries of boxes represent the 75th and 25th percentiles, and bars above and below the boxes indicate the 90th and 10th percentiles, respectively.

In hypertensive individuals, all-cause mortality was lower in extreme dippers compared with that in dippers.[12] Nevertheless, in older hypertensives, the incidence rates of silent cerebral ischemia and stroke were higher in extreme dippers compared with those in dippers.[13] We also demonstrated that CAVI was higher in extreme dippers than in nondippers in a group of normotensives with components of MS. There was also a trend toward higher CAVI in extreme dippers compared with that in dippers. Although the prognostic significance of an extreme dipping status remains a matter of debate, findings from the present study suggest that the extreme dippers have worse metabolic profile (i.e., hypertriglyceridemia) and stiffer arteries (i.e., increased CAVI) compared with the dippers and nondippers. It was suggested that extreme dipping in treated hypertensives is induced by antihypertensive agents.[30] In the present study, we observed an approximately 18% prevalence rate of extreme dipping in a group of normotensives who had never been treated with antihypertensive agents. It is thus speculated that arterial stiffness is a possible mechanism for extreme dipping in normotensives and, in turn, may be responsible for the increased incidence of cerebrovascular events.

Arterial stiffness is mainly caused by aging-induced structural changes. However, arterial stiffness may have been resulted from endothelial dysfunction because the endothelial cells generate

several biological mediators that influence the tone and structure of the blood vessels.[31] For example, both nitric oxide (NO) and endothelin-1 play crucial roles in the regulation of basal vascular tone and BP and may regulate arterial stiffness and wave reflection. NO is synthesized by the endothelium from the amino acid L-arginine by means of the action of the enzyme NO synthase and diffuses to the underlying vascular smooth muscle and causes vasodilatation.[32] Endothelin-1, an extremely potent vasoconstrictor, is a 21−amino acid peptide produced by vascular endothelial and smooth muscle cells.[32] Thus, CAVI as a measure of arterial stiffness may provide a noninvasive surrogate marker of endothelial dysfunction.

A reverse dipping pattern has been suggested to be associated with increased arterial stiffness.[33] In the present study, we were unable to detect the reverse dipping pattern in any one of the study participants. Thus, the question of whether reverse dippers have stiffer arteries than extreme dippers could not be answered.

4.1. Study limitations

First, a noticeable limitation of this study was that the study used a relatively small sample size. Second, the study sample was not homogenous as a group because it comprised 67% of diabetics and 33% of nondiabetics. Cautions must be taken when generalizing findings from this study to other populations. Nevertheless, diabetics and nondiabetics were comparable in clinic BP, ambulatory BP profiles, anthropometric measurements, metabolic profiles, and CAVI values. The three dipping groups were also comparable in the proportion of diabetics.

Third, the information on antidiabetic medications was not available for analysis. Finally, the GISSI score used in this study was calculated based on a European population. The use of GISSI score in Asian populations has not been validated.

In conclusion, MS is associated with neither arterial stiffness nor an abnormal pattern of nocturnal BP reductions in normotensives. However, in normotensive individuals with components of MS, an extreme BP dipping pattern may not be a benign phenomenon because of its association with increased arterial stiffness. Ambulatory BP monitoring may therefore provide useful information for stroke risk in individuals with components of MS.

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