Blood Pressure Pattern during Sleep-Wake Cycle in Subjects with Metabolic Syndrome

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SUMMARY

The reduction of nocturnal drop in blood pressure correlates with a higher risk of cardiovascular complications. In addition, the metabolic syndrome (MS) significantly increases cardiovascular risk. We conducted a descriptive, cross-sectional study to evaluate the pattern of nocturnal drop in blood pressure and other parameters provided by 24-hour ambulatory blood pressure monitoring (ABPM), such as mean daytime and nighttime systolic, diastolic and pulse pressures in subjects with MS, and to determine the relation with the components of this syndrome. A total of 125 patients were included, with ABPM reproducibility pattern. Glycemia, HDL-cholesterol, triglycerides, office blood pressure and abdominal circumference were determined. The presence of MS was defined using the ATP III criteria. The global prevalence of hypertension, MS and non-dipper pattern was 43%, 56% and 44%, respectively. Blood pressure values and the percentage of patients with non-dipper pattern were higher in patients with more components of the metabolic syndrome. The abdominal circumference was the only parameter that predicted the non-dipper pattern. Subjects with MS showed a significant increase in the different blood pressure parameters evaluated by ABPM and a higher prevalence of the non-dipper pattern.

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Key words > Blood Pressure - Metabolic Syndrome - Hypertension - Obesity

Abbreviations >

ATP III	Adult Treatment Panel III	**BP**	Blood pressure
AC	Abdominal circumference	**DBP**	Diastolic blood pressure
HDL-C	High density lipoprotein cholesterol	**SBP**	Systolic blood pressure
HBP	High blood pressure	**PP**	Pulse pressure
BMI	Body mass index	**MS**	Metabolic syndrome
AMBP	Ambulatory blood pressure monitoring	**TGL**	Triglycerides

BACKGROUND

The metabolic syndrome (MS) is a combination of cardiovascular risk factors, such as high blood pressure (HBP), dyslipidemia, obesity, and impaired glucose tolerance, which considerably increases the risk. (1) This combination of factors amplifies the harmful effects of HBP on the arteries because it increases vascular stiffness (2) and multiplies the risk for cardiovascular complications. (3)

At present, blood pressure (BP) recording with the sphygmomanometer is one of the essential tools of physical exam, and continues to be the reference technique, (4) but more and more evidences show that these ocassional BP readings are not representative of its true circadian pattern, and that ambulatory BP monitoring (AMBP) correlates better with target organ damage and cardiovascular events. (5, 6)

The circadian pattern is characterized by reduced nocturnal BP and its elevation during waking hours. In adults, the loss or attenuation of physiological BP reduction at night is an accurate predictor of cardiovascular complications and development of hypertrophy of left heart chambers. (7) Different studies have evidenced that HBP should not be considered an isolated event, because the metabolic disorders associated with it play an important role in the occurrence and long term prognosis of this condition. (8)

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The purpose of this research was to study BP reduction pattern during overnight sleeping hours and other parameters that AMBP causes –such as the daily and night mean systolic, diastolic, and pulse pressures– in individuals with MS, and to evaluate its relationship with the components that define it according to the Adult Treatment Panel III (ATP III).

MATERIAL AND METHODS

Descriptive, cross-sectional study design consisting of purposive sampling, which prospectively selected patients who attended the Specialized Consultation of Preventive Medicine in a Private Health Center in Valencia city, State of Carabobo, Venezuela, between July 2008 and July 2009. Patients were asked to sign an informed consent, and the study was approved by the Ethics Committee of that center. (9)

The study included adult patients over 30 years of age who did not show intolerance to the AMBP procedure, secondary HBP to kidney diseases, endocrine diseases (pheochromocytoma, Addison's disease, acromegaly, uncontrolled diabetes mellitus) and previously diagnosed severe chronic conditions (liver failure or cancer), as well as acute stress situations (sepsis, myocardial infarction), acute infections, obstructive sleep apnea syndrome, and low prescription of sedative medications. In addition, patients who were unable to stop their physical exercise sessions during the AMBP period were excluded, since it may interfere with BP measurements. Pregnant women, drug and alcohol addicts, patients with pathologies associated with changes in autonomic function that potentially affect BP variability (heart failure, coronary artery disease, history of stroke) were also excluded from the study. For the same reason, patients with night working hours were also excluded. With the aim of distributing those patients who accepted to participate in the study according to their MS, their abdominal circumference (AC) was measured with a non-stretch tape measure, graded in millimeters (mm), taking into account the abdominal medial zone, between the iliac crest and the last costal arch, (10) with the subject in standing position and at the end of expiration. Office BP was measured using the ausculatory method, with a callibrated instrument properly validated and according to the internationally accepted protocol. (11) Subsequently, after fasting for 10-12 hours, they had a venous blood draw to determine glucose, high densitiy lipoprotein cholesterol (HDL-C) and triglicerides (TGL) in serum. Serum levels of glucose and TGL were measured by standardized enzymatic colorimetric methods in a Stat fax Omega Iv analyzer. HDL-C concentration was determined with the precipitation method, using the same analyzer. In order to classify patients according to the presence of MS, the criteria established by the ATP III (12) were considered, (12) which state high blood pressure as one of the MS components, based on office BP.

An AMBP was performed on two different ocassions to each participant of the study (with a 4-week interval), with a validated automatic measurement device (Mobil-O-Graph NG 24/48h ABPM). (13) BP measurement was programmed with a frequency of a daily measurement every 15 minutes, and every 20 minutes at nighttime (6). The patient was asked to continue with his/her regular activities, being careful not to submerge the device in water, to hold the arm still while reading is in process, and not to desconnect the equipment until the 24-hour period since the beginning of the recording is over. Only patients with reproducible AMBP pattern were included in the study.

For data analysis, day and night periods were considered separatedly: between 8 a.m. and 8 p.m. during the day, and 11 p.m. to 6 a.m. at night. The AMBP was considered valid when errors were lower than 20%, recordings were not missed for more than two hours, and more than 50 measurements were useful. (14) Criteria used were those established by the 2007 clinical practice guideline of the European Societies of Hypertension and Cardiology (15) for the evaluation of BP control. In the clinic, BP was considered controlled when the 24-hour AMBP revealed mean pressure levels < 130/80 mm Hg. Pulse pressure (PP) (in mm Hg) was calculated as the difference between systolic BP (SBP) and diastolic BP (DBP).

Depending to the results obtained from the average of both AMBP, patients were classified according to their night BP reduction into two categories: dipper (between 10% and 20% systolic and diastolic BP reduction) and non-dipper (when its mean SBP or DBP did not fall at least 10% during sleep from that shown in waking hours). (6) There was no BP fall > 20% or hyper-dipper pattern.

Statistical analysis

Results were expressed as mean ± standard deviation for continuous variables, and as frequencies shown in mean values for qualitative variables. The distribution of the different variables by the Kolmogorov-Smimov test was analyzed. Student t or Mann-Whitney U tests were used (depending on the distribution of variables) to compare the mean values between individuals with or without MS, and the chi square test was used for categorical variables. To evaluate the isolated influence of each of the variables considered to establish MS according to ATP III at risk for an abnormal fall of night BP or non-dipper pattern, a maximum likelihood logistic regression analysis was performed, including age, sex, and only the variables that define MS but are not related with BP. All the tests were performed at a bilateral statistical significance level of 0.05, with the statistical package SPSS 15.0.

RESULTS

After excluding 83 patients who did not show a reproducible AMBP pattern, the number of patients enrolled in the study was 125. The total group mean age was 55.0 ± 11.8 years, with a prevalence of female patients (64.8%). A 20% of them were diabetics, 36.8% were overweight, 68.8% had abdominal obesity, 54 patients said they had hypertension (43.2%), seven of which were not treated, and 56% of them were diagnosed with MS. In 70 patients studied, dipper pattern was observed, whereas 55 patients (44%) did not show this pattern.

Comparison of the patients studied according to the presence of MS (Table 1) showed that mean values of DBP and PP in 48 hours, as well as (day and night) SBP, DBP, and PP were significantly higher in patients with MS. As expected, MS patients showed the clinical and metabolic disorders defined by the ATP III criteria. Also, the proportion of patients with non-dipper pattern was significantly higher in those with MS. No substantial differences between the age of the studied groups were observed, nor when comparing the distribution by sex in both groups.

A progressive increase of all the arterial pressures was detected when the number of MS components

Table 1. Characteristics of the sample studied according to the presence or absence of metabolic syndrome.

Variables	Without MS (n = 55)	With MS (n = 70)	p
Sex (%) (F/M)	33 (60)/22 (40)	48 (69)/22 (31)	0.391
Age (years)	53.7 ± 10.6	56.4 ± 12.6	0.281
AC (cm)	88.0 ± 9.1	100.1 ± 10.4	< 0.001
Glycemia (mg/dl)	86.9 ± 10.1	98.9 ± 21.9	< 0.001
HDL-C (mg/dl)	46.2 ± 5.3	41.2 ± 6.0	< 0.001
TGL (mg/dl)	137.4 ± 37.5	176.6 ± 74.6	< 0.001
OSBP (mm Hg)	118.6 ± 3.7	124.6 ± 8.5	< 0.001
ODBP (mm Hg)	77.6 ± 4.6	82.9 ± 8.3	0.005
Dipper (n)	50 (90.9)	20 (28.6)	< 0.001
Non-dipper (n)	5 (9.1)	50 (71.4)	< 0.001
Mean blood pressure (mm Hg)			
MSBP 48 h	118.0 ± 10.3	127.6 ± 16.2	< 0.001
MDBP 48 h	78.8 ± 5.8	80.3 ± 11.1	0.355
MPP 48 h	42.3 ± 9.8	47.9 ± 11.1	0.003
Daily mean blood pressure (mm Hg)			
D MSBP	122.5 ± 10.8	129.3 ± 16.5	0.009
D MDBP	77.6 ± 7.4	81.6 ± 9.9	0.014
D PP	43.2 ± 11.6	48.6 ± 11.5	0.012
Night mean blood pressure (mm Hg)			
N MSBP	108.9 ± 11.4	119.6 ± 14.5	< 0.001
N MDBP	72.6 ± 14.5	78.6 ± 9.9	0.011
N PP	38.9 ± 8.9	46.6 ± 10.9	< 0.001

MS: Metabolic syndrome. F: Female. M: Male. AC: Abdominal circumference. HDL-C: High density lipoprotein cholesterol. TGL: Triglycerides. OSBP: Office systolic blood pressure. ODBP: Office diastolic blood pressure. MSBP 48 h: Mean systolic blood pressure in 48 hours. MDBP 48 h: Mean diastolic blood pressure in 48 hours. MPP 48 h: Mean pulse pressure in 48 hours. D MSBP: Daily mean systolic blood pressure. D MDBP: Daily mean diastolic blood pressure. D PP: Daily pulse pressure. N MSBP: Night mean systolic blood pressure. N MDBP: Night mean diastolic blood pressure. N PP: Night pulse pressure. Values expressed as mean ± standard deviation. Frequencies expressed in percentages between brackets, for the sex.

increased (Table 2). The percentage of patients according to the distribution of BP reduction pattern differed substantially in patients with different number of MS components (Figure 1).

When relating the nocturnal BP reduction pattern and the presence of MS, there was a trend to the association (OR: 61.8, CI 95%: 13.8-77.3; $p < 0.001$). The applied logistic regression analysis revealed that only the AC was able to predict a non-dipper pattern in the studied individuals (Table 3). The model showed a capacity of prediction of 81.6%.

DISCUSSION

In 44% of the studied individuals, results evidenced a circadian profile that did not show an appropriate BP reduction during the night or resting hours. The frequency of non-dipper pattern was most evident in individuals who had more than three factors for MS at the same time, and the frequency of this pattern in individuals with four and five factors reached 61%. These results match those reported by Hermida et al, (16) who found a significant association of such pattern with the presence of MS in non-diabetic patients and in untreated hypertensives, in a multiple logistic regression model adapted by age, serum creatinine, and smoking habit. Hassan et al (17) also obtained similar results in Omani subjects by using the criteria of the International Diabetes Federation to establish MS. However, it should be noted that such association has not always been evidenced. (18)

It has been documented that clinical outcomes and prognosis of MS patients are related to the number of present components of the syndrome. (19) Vyssoulis et al (20) found that when the number of MS components established by the ATP III increased, the prevalence of dippers decreased significantly, and all the BP values determined by AMBP increased continuously in hypertensive patients. These findings match the outcomes obtained in the present work. Similar findings have also been reported when using

a MS score based on the addition of points assigned to different intervals that adopted seven risk factors or components. (21) The evidences found suggest that variations of BP components and circadian profile would be graduated according to the number of MS components, which would mean that AMBP may be indicated not only in patients with HBP as one of the factors, but also in those with three or more MS components.

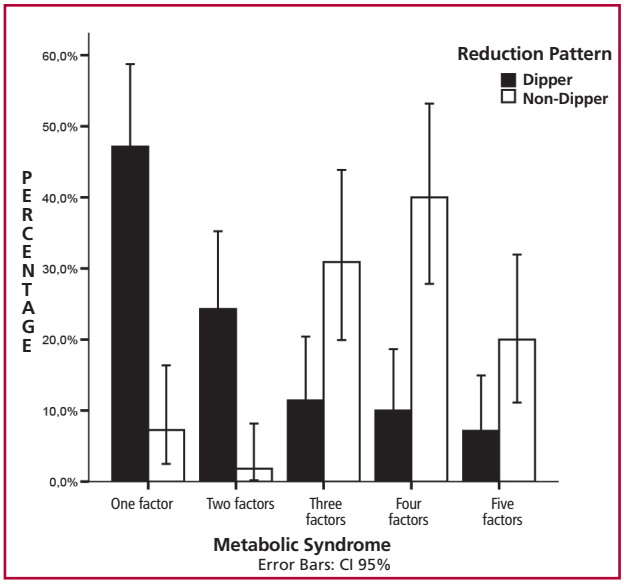

Fig. 1. Percentage of patients with reduced dipper and non-dipper pattern, stratified according to the number of components that define the metabolic syndrome. Values expressed in frequency (%).

It proved not only an increase in mean SBP, and day/night SBP and DBP in individuals with MS, but also a significant increase of PP. These outcomes are consistent with other works (16, 22) and contribute to explain the high cardiovascular risk associated with MS. In this regard, indicators of target organ damage (cardiac hypertrophy, kidney damage) have been positively correlated with SBP and PP obtained through AMBP.

(23, 24) The absence of night BP reduction is related with worse cardiovascular prognosis and target organs damage (25, 26), and it has been demonstrated that night SBP reduction is linked to a lower risk of cardiovascular events, compared with those subjects who do not have such physiologic reduction. (27, 28)

It is important to know which of the MS components –as defined by ATP III– predicts this type of pattern, and the AC was evidenced in the present study.

Previous findings have shown abdominal obesity as the single factor that significantly predicted a decline in the awake SBP/asleep SBP rates, an ongoing indicator that is also used to detect the lack of asleep BP decline; (16) in another study, it was observed that BMI index and TGL levels were determinant of non-dipper pattern.

(16) Ukkola et al (29) related the decline of non-dipper pattern to abdominal obesity and insuline resistance associated to the excess of visceral fat tissue, and attributed the initial damage of target

Table 2. Trend in AMBP parameters according to the number of components that define the metabolic syndrome.

Parameters (mm Hg)	Number of MS components				
	One (n = 37)	Two (n = 18)	Three (n = 40)	Four (n = 18)	Five (n = 12)
Mean BP 48 h					
MSBP 48 h	117.6 ± 9.7	118.9 ± 11.6	122.6 ± 13.7	130.6 ± 15.1	139.6 ± 19.1
MDBP 48 h	78.9 ± 5.9	78.6 ± 5.9	76.4 ± 9.3	82.9 ± 8.1	89.5 ± 14.3
MPP 48 h	41.2 ± 9.0	44.5 ± 11.0	46.6 ± 10.1	49.8 ± 13.0	49.6 ± 11.8
Daily mean BP					
D MSBP	122.1 ± 10.3	123.3 ± 11.9	125.2 ± 14.9	132.1 ± 14.0	139.1 ± 21.0
D MDBP	77.6 ± 8.1	77.6 ± 6.1	79.2 ± 8.4	82.1 ± 5.9	88.8 ± 15.6
D PP	41.8 ± 11.4	46.2 ± 11.8	47.4 ± 10.7	50.1 ± 13.2	50.3 ± 12.3
Night mean BP					
N MSBP	108.1 ± 10.1	110.8 ± 13.7	115.9 ± 13.9	123.4 ± 14.2	125.9 ± 14.2
N MDBP	72.3 ± 13.8	73.2 ± 16.3	77.0 ± 8.2	78.7 ± 7.8	83.4 ± 15.7
N PP	38.1 ± 8.3	40.6 ± 10.4	45.0 ± 9.8	49.2 ± 13.3	48.0 ± 10.6

MS: Metabolic syndrome. BP: Blood pressure. MSBP 48 h: Mean systolic blood pressure in 48 hours. MDBP 48 h: Mean diastolic blood pressure in 48 hours. MPP 48 h: Mean pulse pressure in 48 hours. D MSBP: Daily mean systolic blood pressure. D MDBP: Daily mean diastolic blood pressure. D PP: Daily pulse pressure. N MSBP: Night mean systolic blood pressure. N MDBP: Night mean diastolic blood pressure. N PP: Night pulse pressure. Values expressed as mean ± standard deviation.

Table 3. Logistic regression model for non-dipper pattern of blood pressure in the studied group.

Encounters attended:	ß	Significance	Odds ratio	CI 95% Borderline low – Borderline high
Constant	–15.246	< 0.001	–	–
Age (years)	1.186	0.111	0.09	0.99-1.06
Sex	0.019	0.210	0.43	1.35-8.43
AC (cm)	0.147	< 0.001	1.16	1.08-1.24
Glycemia (mg/dl)	–0.420	0.484	0.54	0.99-1.01
HDL-C (mg/dl)	2.001	0.507	1.02	1.03-1.62
Triglycerides (mg/dl)	1.232	0.145	0.10	0.29-1.56

ß: Regression coefficient. CI 95%: Confidence intervals. Variables included in the model: age, sex, abdominal circumference (AC), glycemia, HDL-C, and triglycerides.

organs and lower reduction of fat tissue to the treatment of the excessive hypertensive load that obese and hypertensive patients suffer. (30) Patients with MS show target organ damage more frequently (left ventricular hypertrophy, carotid intima-media thickness, and microalbuminuria), (31) increased carotid-femoral pulse wave velocity, (22) and more subclinical atherosclerotic carotid lesions (32) than patients who do not have the syndrome. In MS, there is a significant multifactorial, endothelial dysfunction, manifested by predominant vasoconstrictor response, which increases blood pressure and peripheral vascular resistance. (33) This fact is explained by the changes in the thromboxane A2 synthesis, prostacyclin, nitric oxide, and final advanced glycation end products. (33) Insulin resistance could explain the abnormal nocturnal BP reduction pattern associated to MS, since it is considered that this hormone increases BP by the activation of the sympathetic nervous system, the stimulation of the renin-angiotensin system, and the induction of the smooth muscle cells proliferation in blood vessels, which may alter the structure and function of the arteries. (33) Also, hyperleptinemia observed in MS may be an important factor to be considered, since –regardless of BMI– serum leptin concentrations have been directly related to BP evaluated with AMBP in normotensive women with android fat distribution (abdominal obesity). (34) Higher leptin levels in subjects with MS who show non-dipper pattern have also been found. (17) Leptin is able to influence nitric oxide and natriuresis production; this action, together with the chronic sympathetic activation produced particularly in the kidneys, may cause sodium retention, vasoconstriction, and increased BP. (35) Finally, BP changes associated with MS may be related to decreased adiponectin levels observed in MS patients. This hormone not only stimulates the nitric oxide production, but also inhibits the activity of the central nervous system, whose hyperactivity may cause hypertension by raising heart rate and peripheral vascular resistance. (33) Della Mea et al (36) have shown lower values of adiponectin in hypertensive patients who have a non-dipper pattern.

Although this is not a prevalence study, a 56% of MS deserves a comment, since it duplicates the percentage found in Latin American countries included in the CARMELA study. (37) The frequency of MS matches what was reported by another work carried out in the Northern area of Valencia city, Venezuela; (38) however, since the present study did not aim at estimating the prevalence of MS, and the outcome may correspond to a strictly local situation, the data should be taken with caution. Still, the evidence guides to carry out studies about lifestyle and dietary intake in our population, since it has been proved that substantial changes in lifestyle –including exercise and diet changes– are the cornerstone in the treatment of metabolic disorders.

Limitations

Limitations of this work result from the sample size, which is a low number of subjects with four or five MS components. Similarly, the inclusion of individuals was performed on the basis of pragmatic selection criteria, and female subjects were predominant in the assessed group. However, the use of a reproducible AMBP pattern in 48 hours could ensure the reliability and the possibility to compare the results obtained, getting closer to the distribution of general population with cardiovascular risk factors coexisting in MS.

CONCLUSIONS

The study, conducted in a group of SM individuals, showed a significant increase of the different BP parameters evaluated through the AMBP, as well as increased frequency of non-dipper pattern among MS individuals, which was more evident when

the increased number of MS components present. Prospective clinical trials will confirm the reported evidence.

RESUMEN

Evaluación del patrón de presión arterial durante el ciclo vigilia/sueño en individuos con síndrome metabólico

La atenuación del descenso fisiológico de la presión arterial durante la noche se asocia con complicaciones cardiovasculares. Asimismo, el síndrome metabólico (SM) eleva considerablemente el riesgo cardiovascular. El presente estudio, de carácter descriptivo-transversal, se llevó a cabo con el objetivo de evaluar el patrón de descenso de la presión arterial durante el sueño nocturno y otros parámetros que proporciona el monitoreo ambulatorio de la presión arterial (MAPA), como los promedios diurnos y nocturnos de las presiones sistólica, diastólica y del pulso, en individuos con SM y determinar su relación con los componentes que definen a este síndrome. Se incluyeron 125 pacientes adultos con patrón reproducible del MAPA. Se determinaron glucemia, colesterol HDL y triglicéridos en suero, la presión arterial de consultorio y la circunferencia abdominal. Para establecer la presencia de SM se aplicaron los criterios del ATP III. La prevalencia global de hipertensión, de SM y de patrón de descenso de presión arterial non-dipper fue del 43%, 56% y 44%, respectivamente. Se observó un aumento progresivo de todas las presiones arteriales y del porcentaje de pacientes con patrón non-dipper al elevarse el número de componentes del SM presentes en los pacientes evaluados. Sólo la circunferencia abdominal predijo el patrón non-dipper. Se demostró una elevación significativa de los diferentes parámetros de la presión arterial evaluados a través del MAPA, así como una prevalencia incrementada de patrón non-dipper entre los individuos con SM.

Palabras clave > Presión arterial - Síndrome metabólico - Hipertensión - Obesidad

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