Association between metabolic syndrome and parameters of 24-hour blood pressure ambulatory monitoring

Associação entre síndrome metabólica e parâmetros da monitorização ambulatorial da pressão arterial de 24 horas

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ABSTRACT

Objective: To investigate associations between metabolic syndrome (MS) and 24-hour blood pressure parameters as a measure of cardiovascular risk (CVR). **Subjects and methods:** 136 hypertensive subjects, of both sexes, aged between 29 and 83 years were studied. CVR was defined as having at least three of the following conditions: 1) systolic/diastolic blood pressure (BP) $\geq$ 140/90 mmHg, absence/atennuation of nighttime fall in BP during sleep, pulse pressure (PP) $\geq$ 53 mmHg; 2) 24-h PP > 53 mmHg, 3) nighttime PP > 53 mmHg, 4) daytime PP > 53 mmHg and 5) nighttime fall in BP during sleep. **Results:** The 24-h PP, daytime PP and nighttime PP were elevated in 54% of the population. Hypertriglyceridemia (52%), low HDL (72.8%), abdominal obesity (60.3%), MS (58.1%), dyslipidemia (88.8%), overweight (74.3%) and obesity (33.8%) were also elevated. Age-adjusted MS was associated with higher CVR (OR = 4.5 and 3.6), 24-h PP (OR = 2.3 and 4.7), and daytime PP (OR = 2.2 and 4.6). **Conclusions:** MS was highly prevalent and correlated with altered 24-hour blood pressure parameters. Arq Bras Endocrinol Metab. 2011;55(6):383-8

Keywords
Ambulatory blood pressure monitoring; arterial hypertension; cardiovascular risk; pulse pressure

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RESUMO

Objetivo: Investigar associação entre síndrome metabólica (SM) e parâmetros da monitorização da pressão arterial de 24 horas (MAPA) como medida de risco cardiovascular (RCV). **Sujeitos e métodos:** Foram estudados 136 pacientes hipertensos, ambos sexos, idade entre 29 e 83 anos. RCV foi definido pela presença de, no mínimo, três das seguintes condições: 1) pressão arterial sistólica/diastólica $\geq$ 140/90 mmHg, ausência/atenuação do descenso noturno e pressão de pulso (PP) $\geq$ 53 mmHg, 2) pressão de pulso 24h (PP24h), 3) sono (PPS), 4) vigília (PPV) e 5) descenso noturno. **Resultados:** PPV, PPS e PP24h estiveram aumentadas em 54% dos pacientes. Hipertrigliceridemia (52%), HDL baixo (72,8%), obesidade abdominal (60,3%), SM (58,1%), dislipidemia (88,8%), sobrepeso (74,3%) e obesidade (33,8%) estavam elevados. SM, ajustada pela idade, foi associada a elevado RCV (OR = 4,5 e OR = 3,6), a PP24h (OR = 2,3 e OR = 4,7) e a PPS (OR = 2,2 e OR = 4,6). **Conclusões:** SM foi altamente prevalente e correlacionada aos parâmetros da pressão arterial de 24 horas alterados. Arq Bras Endocrinol Metab. 2011;55(6):383-8

Descritores
MAPA; hipertensão; risco cardiovascular; pressão de pulso

INTRODUCTION

Evidence has shown that blood pressure (BP) measurements obtained during a 24-hour period by means of ambulatory blood pressure monitoring (ABPM), especially BP measured during sleep, are better predictors of cardiovascular events (such as myocardial infarction and cerebral vascular accident, including target organ damage) than sporadic BP measurements taken at the physician's office (1-5).

This predictive ability is related to several factors, such as the possibility of identifying individuals with white-coat or masked hypertension. Thus, narrow variations in BP during nighttime and daytime have high prognostic power for clinical outcomes. Some studies revealed greater probability of target organ damage in the absence of at least 10% drop in BP between daytime and nighttime periods (6-10).

Another important prognostic marker in individuals older than 55 years of age is pulse pressure (PP). In a study conducted on 2,010 patients, it was observed that the occurrence of cardiovascular events was 19% and 81% greater in the second and third tertiles of 24-hour BP measurements than in the first tertile (11).

The objective of the present study was to estimate the associations between metabolic syndrome (MS) and 24-hour blood pressure measurements in a sample of hypertensive subjects in a Health Care Center of Belo Horizonte, Brazil.

SUBJECTS AND METHODS

This was a cross-sectional study conducted in outpatient practice for hypertensive patients treated at the Hospital das Clínicas, Universidade Federal de Minas Gerais, and linked to programs on education, self-care, control, and secondary prevention of disease, and to the Family Health Program in the city of Belo Horizonte, in Brazil.

All patients from the programs cited above were invited to participate in this study. At the end of recruitment period, the sample was composed of 136 patients aged between 29 and 83 years old, of both sexes, who were undergoing regular monitoring by these programs. They also had clinical diagnosis of arterial hypertension confirmed by physicians in these services. Participants could either be on drug therapy or not, and had to present stable clinical conditions at the moment of data collection.

Data were collected by trained nurses during an outpatient appointment. According to the protocol, BP was measured three times with a mercury sphygmo-

manometer during evaluation, with 5-minute intervals between measurements, before the 24-hour pressure monitor was set in place.

Based on these measurements, patients were classified into two groups, according to the median of their blood pressure: controlled hypertensive patient (normal: < 140 mmHg for systolic BP and < 90 mmHg for diastolic BP) and uncontrolled hypertensive patient (≥ 140 mmHg for systolic BP and ≥ 90 mmHg for diastolic BP) (12).

The following patients were excluded from the study: pregnant women and patients with neoplasms, psychiatric illnesses, morbid obesity (Body Mass Index, BMI ≥ 35 kg/m^2), acute coronary syndrome, cardiac failure, cerebral vascular accident, congestive cardiac failure, and hypertensive crisis detected at the moment of BP measurement. The last item was characterized by symptoms such as cephalea, malaise, dizziness, blurred vision, thoracic pain, palpitations, breathing difficulty, and arterial pressure > 200/120 mmHg (12). In this last case, the patient was immediately sent to the emergency room.

The 24-hour BP measurements were recorded using a continuous blood pressure monitor (model 90207-30, Spacelabs Inc, Redmond, WA, USA). The device was placed on the non-dominant upper limb of the patient between 2 p.m. and 6 p.m., and was removed 24 hours later. The device was programmed to record BP readings every 20 minutes during daytime (6 a.m. to 10 p.m.) and every 30 minutes during nighttime (10 p.m. to 6 a.m.), with a maximum of 64 readings. Only data from patients who presented enough readings were included. A satisfactory number of readings were obtained from 144 patients. Of these, eight were excluded due to technical problems in the readings. Thus, the final sample was composed of 136 patients.

Pulse Pressure was determined by subtracting mean diastolic BP from mean systolic BP. PP values greater than 53 mmHg were considered as high risk for cardiovascular events (11). Nighttime fall in BP, characterized by a drop in systolic and diastolic BP during sleep (13), was calculated from the formula proposed by Ohkubo e cols. (14) [(mean daytime pressure – mean nighttime pressure) / (mean daytime pressure) x 100]. Nighttime fall in BP was classified as moderate when values were less than 10% (non-dippers), absent when it was 0% (non-dippers), and normal when greater than or equal to 10% (dippers).

In order to characterize patients with desirable outcomes, individuals had to present at least three of the following conditions: mean 24-hour systolic BP ≥ 140 mmHg, mean 24-hour diastolic BP ≥ 90 mmHg, ab-

sent or moderate nighttime fall in BP (non-dipper), or PP > 53 mmHg. In addition to this outcomes, three others were studied: 24-hour PP > 53 mmHg; PP during sleep > 53 mmHg; and daytime PP > 53 mmHg.

Two age categories were created: 29 to 59 years and 60 to 83 years. These two groups were formed based on greater alteration observed in the outcomes of individuals aged 60 years or older (15). Body Mass Index (BMI = weight/height^2) was divided into overweight (BMI ≥ 25.0 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) (16). Abdominal obesity was determined according to the parameters of the National Cholesterol Education Program (17), based on the measurement of waist circumference, with cutoff points of 102 cm for men, and 88 cm for women. MS was defined by the presence of at least three of the following situations: abdominal obesity (described above), hypertriglyceridemia (triglycerides ≥ 150 mg/dL), low HDL (< 50 mg/dL for women and < 40 mg/dL for men), arterial hypertension (systolic BP ≥ 130 mmHg, diastolic BP ≥ 85 mmHg, or use of antihypertensive drugs), and fasting glucose ≥ 100 mg/dL, or use of oral antidiabetic agents/insulin (18).

In the laboratory, serum and plasma samples were analyzed using a regularly calibrated Roche COBAS MIRA PLUS chemistry analyzer. Total cholesterol, triglycerides, and glucose were determined using an enzymatic colorimetric test. Concentration of high-density lipoprotein, HDL-c, was also measured by means of an enzymatic colorimetric test, followed by precipitation of LDL-c and VLDL-c fractions with phosphotungstic acid and magnesium chloride. LDL-c concentrations were calculated by Friedewald equation, LDL-c = TC − (HDL-c + TG/5), in which TC represents total cholesterol, and TG, triglycerides (19). Dyslipidemia was determined by the guidelines of the National Cholesterol Education Program (17), and was detected based on the presence of at least one alteration in serum lipid values.

Bivariate logistic regression analysis was used to test the factors associated with each of these outcomes, taking into account the following independent variables: age, sex, smoking, HDL-c, LDL-c, triglycerides, total cholesterol, fasting glucose, overweight, obesity, abdominal obesity, MS, and dyslipidemia. In order to obtain the association model, a logistic regression equation was applied to each outcome of the circadian cycle of BP, using the stepwise variable selection and discarding variables with p-values > 0.20. In the final association model, only variables with p ≤ 0.05 were considered significant. Strength of the association between variables was estimated by odds ratio (OR) and

95% confidence intervals (95% CI), using the Statistical Package for Social Science (SPSS) 15.0.

The study was approved by the Research Ethics Committee of the Universidade Federal de Minas Gerais. All participants provided written, informed consent, which was freely and spontaneously obtained after all necessary explanations were given.

RESULTS

The sample studied was composed of 136 individuals, 111 women and 25 men. From these subjects, 44% were younger than 60 years of age, 58.6% were married, and 13.5% had no schooling. The vast majority were homeowners (83.8%), and only 36.7% were employed at the time of the interview (data not shown).

Table 1 presents mean values of BP parameters obtained by 24-hour ABPM. Mean values were elevated for 24-hour systolic BP (133.57 mmHg), daytime systolic BP (136.47 mmHg) and nighttime PP (53.44 mmHg), when compared with normal ranges.

The prevalence of cardiovascular, metabolic and anthropometric risk factors were 52% for hypertriglyceridemia, 72.8% for low HDL, 60.3% for abdominal obesity, 58.1% for MS, 88.8% for dyslipidemia, 74.3% for overweight, and 33.8% for obesity. Women presented a higher prevalence of abdominal obesity and dyslipidemia (65.8% and 92.2%, respectively), p < 0.05 (Table 2).

Table 1. Hemodynamic parameters determined via Ambulatory Blood Pressure Monitoring (ABPM). Belo Horizonte, Minas Gerais, Brazil, 2005

Blood Pressure Parameters	n	Mean	SD	Minimum	Maximum
Mean Systolic BP					
24-hour (mmHg)	136	133.57	13.78	106.00	168.00
Daytime (mmHg)	135	136.47	13.87	109.00	175.00
Nighttime (mmHg)	135	127.85	16.80	94.00	191.00
Mean Diastolic BP					
24-hour (mmHg)	136	80.80	8.64	59.00	106.00
Daytime (mmHg)	135	84.11	9.44	64.00	113.00
Nighttime (mmHg)	135	74.41	9.47	51.00	109.00
Mean PP					
24-hour (mmHg)	136	52.77	11.46	32.00	90.00
Daytime (mmHg)	135	52.36	11.49	31.00	89.00
Nighttime (mmHg)	135	53.44	12.89	29.00	100.00
Partial or absolute fall (mmHg)[1]	135	8.61	11.92	-39.00	41.00
Relative fall[2] (%)	135	6.23	8.36	-25.66	28.79

BP: blood pressure; PP: pulse pressure.
[1] Partial or absolute fall = mean daytime systolic pressure − mean nighttime systolic pressure.
[2] Relative fall = [(mean daytime systolic pressure − mean nighttime systolic pressure) / (mean daytime systolic pressure) x 100].

Table 3 shows the final models of the variables associated with the four outcomes, obtained with hemodynamic parameters. Being older than 60 years presented an association with each outcome (OR ranging from 2.68 to 4.74). MS also showed a strong association with 24-hour PP, PP during sleep > 53 mmHg, and with the following groups of variables: increased 24-hour PP, non-dipper pattern, and arterial hypertension, with OR ranging from 2.29 to 4.51. None of the other factors were significantly associated with the outcomes in the multivariate model.

DISCUSSION

The present study evaluated the relationship between metabolic disturbances and the circadian rhythm of BP, obtained by means of ABPM in hypertensive patients. From these parameters, it was possible to characterize individuals with absent or moderate nighttime fall in BP during sleep (non-dipper pattern), patients with elevated PP, and elevated mean 24-hour BP.

The presence of one or more of these factors characterized the clinical outcome. Patients who presented at least three of these conditions had high risk for target organ damage, such as ventricular hypertrophy and microalbuminuria (20). The group of hypertensive patients studied showed that mean 24-hour systolic BP mean daytime systolic BP, mean nighttime systolic BP, and PP were above the normal range. These values were even more elevated in individuals who were 60 years old or older. Similar results were found in other studies involving elderly hypertensive patients (13,21-23).

Metabolic syndrome, diagnosed according to criteria defined by the National Cholesterol Education Program (17), and modified by Grundy and cols., was strongly associated with all parameters of circadian variation of BP evaluated in this study, except for PP during wakefulness. These results remained statistically significant, even after controlling for confounding factors, such as age and sex, in addition to other variables that were excluded from the analysis during modeling.

Table 2. Prevalence of metabolic risk factors according to sex and age. Belo Horizonte, Minas Gerais, Brazil, 2005

Cardiovascular variables[1]	Male	Female	< 60 years	≥ 60 years
	n (%)	n (%)	n (%)	n (%)
Elevated fasting glucose (mg/dL)	06 (27.3)	33 (32.0)	16 (32.2)	23 (31.9)
Hypertriglyceridemia (mg/dL)	06 (27.3)	22 (21.4)	13 (25.0)	15 (21.1)
Low HDL (mg/dL)	13 (59.1)	78 (75.7)	41 (77.4)	50 (69.4)
Elevated LDL (mg/dL)	10 (45.5)	46 (44.7)	26 (50.0)	30 (42.3)
Hypercholesterolemia (mg/dL)	07 (31.8)	52 (50.5)	25 (48.1)	34 (47.9)
Abdominal obesity (cm)	09 (36.0)[2]	73 (65.8)[2]	36 (59.0)	46 (61.3)
Metabolic syndrome (NCEP)[3]	14 (63.6)	58 (56.9)	30 (57.7)	42 (58.3)
Dyslipidemia (NCEP)[4]	16 (72.7)[2]	95 (92.2)[2]	49 (92.5)	62 (86.1)
Overweight (kg/m²)	20 (80.0)	81 (73.0)	48 (78.7)	53 (70.7)
Obesity (kg/m²)	10 (40.0)	36 (32.4)	19 (31.1)	27 (36.0)

[1] Values defined for: elevated fasting glucose ≥ 100 mg/dL; hypertriglyceridemia (triglycerides ≥ 150 mg/dL), low HDL (HDL < 50 mg/dL for women and < 40 mg/dL for men); hypercholesterolemia (total cholesterol ≥ 200 mg/dL); abdominal obesity (WC ≥ 102 cm for men and ≥ 88 cm for women); overweight (BMI ≥ 25 kg/m²); obesity (BMI ≥ 30 kg/m²) (NCEP, 2001).
[2] Likelihood ratio. Statistically significant difference (p < 0.05).
[3] Metabolic syndrome defined by the presence of at least three of the following (cutoff values described for item 1): enlarged waist circumference, hypertriglyceridemia, low HDL, arterial hypertension (Systolic BP ≥ 130 mmHg, Diastolic BP ≥ 85 mmHg, or use of anti-hypertensive medication), and high fasting glucose (NCEP, 2001; Grundy et al., 2005).
[4] Dyslipidemia based on the National Cholesterol Education Program (NCEP, 2001), and detected by the presence of at least one alteration in serum lipid values.
HDL: high-density cholesterol; LDL: low-density cholesterol; BMI: body mass index; WC: waist circumference.

Table 3. Models of variables related to blood pressure circadian cycle. Belo Horizonte, Minas Gerais, Brazil, 2005

Variables	24h PP > 53 mmHg		Nighttime PP > 53 mmHg		Daytime PP > 53 mmHg		24h PP, DIP, AHT[1]	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age	4.74	2.118 - 10.652	4.60	2.028 - 10.445	2.68	1.241 - 5.819	3.63	1.577 - 8.353
Sex	2.17	0.773 - 6.134	2.37	0.816 - 6.926	-	-	0.56	0.199 - 1.632
Metabolic syndrome	2.34	1.061 - 5.189	2.29	1.037 - 5.096	-	-	4.51	1.957 - 10.423
AHT	-	-	-	-	5.33	2.488 - 11.415	-	-

24h PP: 24-hour pulse pressure; nighttime PP: pulse pressure during sleep; Daytime PP: daytime pulse pressure; DIP: dippers; AHT: arterial hypertension.
[1] In this model, individuals presented at least three of the following conditions: Systolic BP ≥ 140 mmHg; Diastolic BP ≥ 90 mmHg; absent or moderate nighttime fall in BP; 24h PP > 53 mmHg.

Individuals with MS presented higher chances, ranging from 2.29 to 4.51, of having altered circadian rhythms of BP. MS and age were not significantly associated with decreased nighttime fall in BP, when tested as an isolated outcome of altered circadian rhythm.

Several studies confirm the relationship between MS and alterations in circadian rhythm of BP (25-28), including individual components such as hypercholesterolemia, hypertriglyceridemia, low levels of HDL, insulin resistance, and abdominal obesity (24). MS is highly prevalent among patients with hypertension (25). In a study with a sample composed of 1,124 Arabs, 50% of the non-dippers were diagnosed with MS, and 30% of the dippers were also hypertensive. In addition, in a cross-sectional study with 1,170 non-treated hypertensive individuals evaluated with 48-hour ambulatory monitoring, PP was significantly higher in patients without nighttime fall in BP (26). Hermida and cols. showed significant associations between MS and the absence of circadian variation in daytime-nighttime BP. In a cohort study of 517 treated hypertensive patients, obesity and insulin resistance – two MS components – independently influenced PP, and this effect was greater in women (28). It is presumed that there are several mediating mechanisms affecting MS for cardiovascular events. One would be caused by the hemodynamic effects of the syndrome, increasing the incidence of pre--clinic cardiovascular events and renal alterations, such as ventricular hypertrophy, microalbuminuria, reduction in aortic elasticity, and carotid arteriosclerosis (29).

Recent studies investigated nighttime fall in PP and BP as independent predictors of cardiovascular risk (3,7,11,30-32). In a cross-sectional study conducted in Rio de Janeiro, Brazil, it was shown that PP had greater predictive power for target organ damage than nighttime fall in BP (6). The PIUMA study showed that morbidity and mortality due to cardiovascular disorders were strongly associated with 24-hour PP in apparently healthy, hypertensive individuals (11,31). However, in some studies, PP was not independently associated with cardiovascular outcomes and other diseases (30,33). Recently, other studies have also shown that PP was significantly associated with an increase in the risk for cerebral vascular accident, coronary heart disease, and congestive cardiac failure. However, predictive value was not higher than systolic BP or diastolic BP (30). Alternatively, some studies indicated that the vast majority of the elderly show isolated or predominant systolic BP elevation which, as a consequence, elevates

PP. Franklin and cols., in a study conducted with the Framingham cohort, suggested that PP could predict cardiovascular risk in older people with greater precision than systolic BP.

In the present study, it was observed that the greater the age, the greater the chance of presenting increased PP during sleep, 24-hour PP, and daytime PP, which increase the risk of developing cardiovascular diseases. These data corroborate the studies by Staessen and cols. and Pickering and cols., and shows that the loss in nighttime fall in BP, increased PP, and increased morning BP, all common among the elderly, are related to increased cardiovascular risk. In the study by Verdecchia and cols., values above 53 mmHg were related to an almost five--fold increase in the occurrence of cardiovascular events.

Several studies suggested the use of BP during daytime, PP, and presence of nighttime fall in BP during sleep as additional stratification of cardiovascular risk among hypertensive patients who are diagnosed via sporadic BP measurements at the physician's office and not treated. However, these variables have not been employed to direct patient treatment, because there are only a few studies addressing these factors, especially in relation to PP. In this context, the present study contributes with new evidence regarding the relationship between MS and the circadian cycle of BP.

Some limitations of the present study must be mentioned. As this is a cross-sectional study, the potentially predictive variables and the outcome variables were obtained simultaneously, which makes it difficult to establish causal or temporal relationships. Studies with prospective designs would enable the observation of changes in the occurrence of cardiovascular diseases and deaths in the presence of risk factors over time. Another limitation consists of the absence of precise data regarding the drug therapy patients adopted during the study. Data concerning the presence or absence of diabetes in the individuals were unavailable and may also be an important limitation, once diabetics are more prone to develop MS. Inadequate control of BP detected in some patients also constitutes an important measurement bias. Although we studied a convenient sample, we found important relationships between MS and 24-hour BP parameters. Finally, the interpretation of the results involving gender differences must be viewed cautiously due to the higher proportion of women (81.6%) compared to men (18.4%) in the study.

In conclusion, our study not only showed high frequency of MS and their components in a outpatient prac-

tice setting, but also emphasized the correlations between this syndrome and 24-hour blood pressure measurements, adjusted by age. Several mechanisms may be involved in this association. Therefore, more effective interventions in the many components and metabolic abnormalities of MS and hypertension are needed, in addition to the negative prognosis of damage to target organs.

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