Ambulatory Blood Pressure Monitoring and Cardiovascular Risk in Resistant Hypertensive Women

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Summary

Background: **Few studies have explored the prognostic value of ambulatory blood pressure (ABP) in resistant hypertensive patients, a high-risk group.**

Objective: **To investigate the prognostic value of uncontrolled daytime ABP in resistant hypertensive women.**

Methods: **We followed 382 resistant hypertensive women, aged 24-92 years, from a hypertension unit of a university hospital, for up to 8.9 years (mean 3.9). Patients were classified as controlled (office BP≥140/90mmHg and daytime ABP <135/85 mmHg) or uncontrolled (office BP≥140/90mmHg and daytime ABP ≥135/85 mmHg). We analyzed a combined endpoint, consisting of cardiovascular mortality, ischemic heart disease, stroke and nephropathy. Cox proportional hazard models were used to estimate the risk for cardiovascular events, adjusting for potential confounders.**

Results: **The total event rate was 5.0 per 100 women-years. In the controlled and uncontrolled groups, the rates were 3.7 vs. 5.8 events respectively, p=0.06. The relative risks adjusted for age and current smoking status associated with a 10 mmHg increment in systolic ABP were greater than the ones associated with a 5 mmHg increment in diastolic ABP. Non-dipper patients had a higher risk for cardiovascular events than dipper patients (RR = 1.42 (0.87 – 2.32)), although this association had no statistical significance. Uncontrolled daytime blood pressure (yes/no) was a stronger independent risk factor, 1.67 (1.00-2.78).**

Conclusions: **There was a 67% increase in the risk of a cardiovascular event if daytime ambulatory blood pressure was uncontrolled in women with resistant hypertension. Therefore, it is mandatory to use ABP to evaluate control and to guide therapeutic strategies in resistant hypertensive patients. (Arq Bras Cardiol 2009; 92(6) : 448-453)**

Key words: **Blood pressure monitoring, ambulatory; hypertension; cardiovascular diseases; prognosis.**

Introduction

Cardiovascular diseases are the main cause of mortality all over the world and an important contributing factor is the difficulty in blood pressure (BP) control. Despite the fact that pharmacological therapy of hypertension is widely spread, the proportion of patients with BP lower than 140/90 mmHg after treatment ranges from 6% to 25%[1].

In the USA, there were no significant changes in the rates of hypertension control for women between 1988 to 1994 and 1999 to 2004, with the rates remaining under 50%, while 50% of men aged 60 and older achieved hypertension control. Possible explanations for the poor blood pressure control seen in women may be the fact that physicians are less likely to suggest preventative measures for women than men, as they significantly minimize the cardiovascular risk status of women when compared with men, as they are not aware that more women than men die annually of cardiovascular diseases[2].

In Brazil, there was a 500% increase in the elderly population in 40 years. There will be 32 millions of elderly subjects by the year 2020. Life expectancy has been rising, and in an overwhelming majority of countries, women outnumber men in later life. However, although females have higher life expectancy than males, they live proportionally fewer years in good health[3,4].

Evidence indicates that ambulatory BP (ABP) measurements are more closely related to target organ damage than office BP measurements[5-9]. Although some studies have explored the prognostic value of ABP in treated hypertensive subjects[10-12], few investigated this issue in resistant hypertensive patients[13], a high-risk group that challenges clinical practice.

The aim of this study was to evaluate the cardiovascular outcome in a cohort of resistant hypertensive women, comparing the ones with controlled daytime ABP with the non-controlled ones.

Methods

The present study design is a cohort of 382 women referred to an outpatient hypertension clinic due to resistant

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hypertension. The exposure was uncontrolled daytime ABP at the entrance of the study and the endpoint was any cardiovascular event.

Resistant hypertension was defined as office BP persistently higher than 140/90 mmHg in spite of triple or more intensive antihypertensive therapy.

Patients gave their informed consent. The study was in accordance with the second Declaration of Helsinki and was approved by the Institutional Review Board.

Clinical evaluation

All patients underwent clinical evaluation, electrocardiography, routine laboratory tests and echocardiographic examination. After optimization of the therapeutic regimen, patients were submitted to ABP monitoring. Secondary hypertension was an exclusion criterion.

The physician measured the patient's office blood pressure in the sitting position, using a calibrated mercury sphygmomanometer with an appropriately-sized cuff. Two BP measurements were taken during the visit (at least 5 min apart) and the second one was used. Weight, height, and waist circumference were determined for each subject; waist circumference was measured at the narrowest diameter between the costal margin and the iliac crest. Body mass index (BMI) was calculated by the weight in kilograms divided by the square of the height in meters.

Risk factors evaluated were: diabetes (two fasting glycemias ≥ 6.9 mmol/L or under treatment), dyslipidemia, current smoking status, overweight/obesity (overweight defined as BMI ≥25 kg/m^2 and obesity as BMI≥30 kg/m^2), sedentary lifestyle (no regular physical activity at least 30 min per day, on most days of the week).

The American Society of Echocardiography criteria for left ventricular hypertrophy (LVH), which considers hypertrophy as a left ventricular mass index (LVMI) >104 g/m^2 for women, was used[14]. LV mass was calculated according to Devereux[15] and normalized for body surface area to obtain the LVMI.

Follow-up

Patients were followed at the outpatient clinics (Hypertension, Internal Medicine, Cardiology, and Geriatrics) of the same hospital. Patients' characteristics and the occurrence of cardiovascular events were recorded during follow-up visits. Patients that did not return after one year and that could not be contacted by telephone were searched at the Mortality Information System.

Cardiovascular events included fatal and nonfatal coronary disease (myocardial infarction, bypass surgery or angioplasty), cerebrovascular disease (stroke, corroborated by physical exam and/or CT scans), and hypertensive nephropathy (proteinuria >500 mg/24 h and/or creatinine clearance <50 ml/min and/or microalbuminuria of 30–299 mg/day).

Ambulatory BP monitoring

Ambulatory BP was recorded using the Oscar (SunTech Medical) or DYNAMAPA equipments, both of which have been approved by the British Society of Hypertension[8]. A reading was taken every 10 min throughout the day and every 20 min at night. The data were considered adequate when a minimum of 70 valid records were obtained in 24 h, with at least two records per hour during the nighttime. Patients registered their sleep patterns, so that an individual nighttime pattern could be entered into the software for each patient[16]. The following parameters were evaluated: average 24-h, daytime and nighttime systolic BP (SBP) and diastolic BP (DBP); pulse pressure (PP) was calculated as systolic minus diastolic BP. Patients were defined as nondippers if they had a reduction in BP less than 10% from daytime to nighttime, or as dippers, when otherwise. Women were classified either as having controlled daytime ABP (white coat resistant hypertension), office BP≥140/90mmHg and daytime ABP <135/85mmHg, or as having uncontrolled daytime ABP (true resistant hypertension), office BP ≥140/90mmHg and daytime ABP ≥135/85 mmHg[7].

Statistical analysis

Data were expressed as mean ± standard deviation or percentage. Baseline characteristics were compared with Mann-Whitney test for continuous variables and χ^2 tests for categorical variables. For the participants who experienced multiple events, the analysis included only the first event. Event rates are expressed as the number of events per 100 patient-years based on the ratio of the observed number of events to the total number of patient-years exposure up to the terminating event or censor. Survival curves were estimated using the Kaplan-Meier product-limit method and were compared by the log-rank test. Variables that had a p value less or equal to 0.20 were included in the multivariate analysis as potential confounders. The independent effect of uncontrolled daytime ABP was tested using multivariate Cox proportional-hazard models. The confounding effect was assessed by the change each variable produced in the point estimate and hazard ratio (relative risk) of the categorical variables controlled /uncontrolled daytime ABP. Effect modification was investigated using a heterogeneity test for an interaction term included in the model. Analyses were carried out using STATA 9.0 (StataCorp, Texas, USA).

Results

Of the 382 patients analyzed, 162 (42.4%) were classified as presenting controlled daytime ABP, and 220 (58.6%) as presenting uncontrolled daytime ABP. The main clinical characteristics and BP values of the patients in each group are shown in Table 1. The controlled group was older and more dyslipidemic than the uncontrolled group, whereas body mass index and circumference waist were higher in the uncontrolled group. Afro-Brazilian patients were slightly more frequent in the uncontrolled group. All others characteristics were similar between the groups. The blood pressure parameters were higher in the uncontrolled group than in the controlled group, except for the pulse pressure that was higher in the controlled group.

Eighty-eight percent of the patients had been prescribed three or four antihypertensive drugs and twelve percent were prescribed more than four. All patients were taking diuretics.

The most frequently used drugs were ACE inhibitors (89.3%), B-blockers (79.1%) and calcium channel blockers (49.0%). The latter was more frequently used by the controlled patients than by the uncontrolled ones. The most frequently used therapeutic regimen in each group is shown in Table 1.

Forty-two subjects (11.0%) were lost to follow-up, 14.6% from the uncontrolled group and 6.2% from the controlled group, p=0.01.

A total of 73 new cardiovascular events were recorded during a mean follow-up period of 3.9 years, ranging from 1 month to 8.9 years, with 1,474.0 person-years at risk. There were 25 fatal and 48 non-fatal cardiovascular events. The total event rate per 100 women-years was 5.0. The incidence rate of events was lower for the controlled group than for the uncontrolled one (3.7 *vs.* 5.8 events per 100 women-years; p=0.06). The probability of event-free survival is presented in Figure 1. The comparison of survival curves among the groups showed that the survival was lower for the uncontrolled than for the controlled group, although the difference was not statistically significant (log-rank p= 0.10). No race/ethnic-based difference in survival was observed.

Only age and current smoking status were considered confounders for the association between daytime ABP control and cardiovascular events in this population.

The relative risks adjusted for age and current smoking status associated with a 10 mmHg increment in systolic ABP and with a 5 mmHg increment in diastolic ABP are reported in Table 2. The relative risks associated with increments in systolic BP were greater than the ones associated with increments in diastolic BP.

Non-dipper patients had a higher risk for cardiovascular events than dipper patients (RR = 1.42 (0.87 – 2.32)), mainly for the uncontrolled patients (RR = 1.70 (0.93 – 3.10)) when compared to the controlled ones (RR = 0.92 (0.40 – 2.15)), although these associations had no statistical significance. There was no interaction between dipper pattern and BP control (p=0.34).

Cox regression analysis showed that daytime ABP control was an independent risk factor for new cardiovascular events, RR = 1.67 (Table 3).

Discussion

The results of our prospective study with resistant hypertensive women showed that, after adjustment for traditional risk factors, the daytime ABP control provided additional prognostic information concerning cardiovascular events.

The incidence rates as well as the survival curve showed a worst risk profile for the uncontrolled patients, although this unadjusted analysis did not show a striking difference. The relative risk after adjustment for age and current smoking status was almost 70% higher in the group with higher daytime BP.

Although the uncontrolled patients had higher BMI and larger waist circumference, these characteristics were not

Table 1 - Characteristics of the population according to controlled/ uncontrolled daytime ABP

Parameter	Uncontrolled	Controlled	P value
N (%)	**220 (57.6)**	**162 (42.4)**	
Demographic variables			
Age (years)	59.1 (12.0)	61.9 (10.8)	0.029
Afro-Brazilian, n (%)	112 (50.9)	68 (42.0)	0.069
Risk factors			
Body mass index (kg/m²)	31.5 (6.1)	30.5 (6.8)	0.026
Current smokers, n (%)	19 (8.7)	10 (6.3)	0.383
Physical inactivity, n (%)	168 (77.4)	119 (74.8)	0.561
Diabetes, n (%)	90 (40.9)	61 (38.4)	0.618
Dyslipidemia, n (%)	132 (61.4)	117 (74.1)	0.010
Subclinical organ damage			
LV Hypertrophy, n (%)	169 (83.3)	118 (78.7)	0.275
Factors for MetS			
Glucose (mmol/L)	6.8 (3.0)	6.5 (2.3)	0.855
Triglyceride (mmol/L)	1.8 (1.4)	1.7 (0.96)	0.887
HDL (mmol/L)	1.2 (0.31)	1.2 (0.32)	0.668
Circumference waist (cm)	101.9 (12.9)	99.1 (12.9)	0.042
Metabolic syndrome, n (%)	51 (31.5)	63 (28.6)	0.55
Office blood pressure			
Systolic (mmHg)	189.2 (30.8)	178.2 (23.8)	0.001
Diastolic (mmHg)	103.3 (19.8)	96.4 (15.7)	0.002
Ambulatory blood pressure			
Systolic daytime (mmHg)	153.5 (16.3)	122.3 (8.9)	<0.001
Diastolic daytime (mmHg)	87.2 (12.6)	70.7 (7.5)	<0.001
Systolic nighttime (mmHg)	143.1 (22.1)	112.8 (13.6)	<0.001
Diastolic nighttime (mmHg)	77.9 (14.3)	62.8 (9.3)	<0.001
Systolic 24-h (mmHg)	151.4 (16.5)	120.4 (8.9)	<0.001
Diastolic 24-h (mmHg)	85.2 (12.6)	69.1 (7.4)	<0.001
Pulse Pressure 24-h (mmHg)	50.2 (8.8)	64.0 (13.4)	<0.001
Dipper, n (%)	113 (51.4)	84 (52.2)	0.876
Therapeutic regimen			0.022
Diur + ACEI + BB	58 (26.4)	39 (24.1)	
Diur + ACEI + CCB	25 (11.4)	20 (12.3)	
Diur + ACEI + BB + CCB	23 (10.5)	36 (22.2)	
Diur + ACEI + BB + VD	32 (14.5)	15 (9.3)	
Others	82 (37.3)	52 (32.1)	

Data are presented as mean ± SD or number (%); LV - left ventricular hypertrophy; HDL - high density lipoprotein; Diur - diuretics; ACEI - angiotensin-converting enzyme inhibitors; BB - B-blockers; CCB - calcium channel blockers; VD - direct vasodilators

Table 2 – **Adjusted relative risks per 10 mm Hg increase in systolic blood pressures and per 5 mm Hg increase in diastolic blood pressures for the combined end point**

Blood Pressures	RR (95% CI)	P value
Ambulatory		
24h-SBP	1.16 (1.03-1.30)	0.02
24h-DBP	1.08 (0.97-1.20)	0.17
Daytime SBP	1.15 (1.02-1.29)	0.03
Daytime DBP	1.07 (0.97-1.18)	0.22
Nighttime SBP	1.12 (1.02-1.23)	0.03
Nighttime DBP	1.08 (0.99-1.19)	0.09
Pulse Pressure (1 mm Hg)	1.02 (1.01-1.04)	0.02
Office		
SBP	1.04 (0.96-1.13)	0.26
DBP	0.97 (0.90-1.04)	0.38

Relative Risks are adjusted for age and current smoking status; SBP – systolic blood pressure; DBP - diastolic blood pressure.

Table 3 – **Relative risks of cardiovascular events associated with daytime ABP uncontrolled: crude and adjusted for age and current smoking status**

	RR (95% CI)	p value
Crude	1.52 (0.92 – 2.51)	0.10
Adjusted	1.67 (1.00 – 2.78)	0.05

RR - relative risk ; CI - confidence interval

associated with cardiovascular risk in this population, probably because these measures were very high in both groups.

The lack of association between dyslipidemia and cardiovascular risk may be due to a survival bias at baseline. Patients with dyslipidemia would be underrepresented in the uncontrolled group, as they would have died earlier.

Calcium channel blocker agents were more frequently used by the controlled patients (older ones), but this agents were not an independent cardiovascular risk factor.

Our results suggest that a dipper pattern may be associated with lower cardiovascular risk, and this association seems to be stronger in patients already at a higher risk due to increased BP levels. Effect modification is plausible and we may not have had the power to detect it.

Our results are in line with other studies carried out in treated hypertensive populations to investigate the prognostic impact of ABP[10-13].

Redon *et al*[13] studied 86 patients with DBP> 100 mmHg using three or more antihypertensive drugs, including a diuretic. After 49 months of follow-up, the risk of a cardiovascular event was significantly higher for patients who had a higher daytime diastolic BP at baseline (RR = 6.2; 95%CI = 1.38-28.1).

Verdecchia *et al*[10] showed that ABP control (daytime) is superior to office BP control when predicting cardiovascular outcome in treated hypertensive patients receiving single, double or multiple therapy. The event rate was lower (0.71 events/100 person-years) among patients with controlled ABP than among those with uncontrolled ABP (1.87 events/100 person-years), p=0.003. When both office and ABP controls were forced into the same model, only ABP control achieved significance, with an adjusted relative risk of 0.36 (95%CI 0.18-0.70).

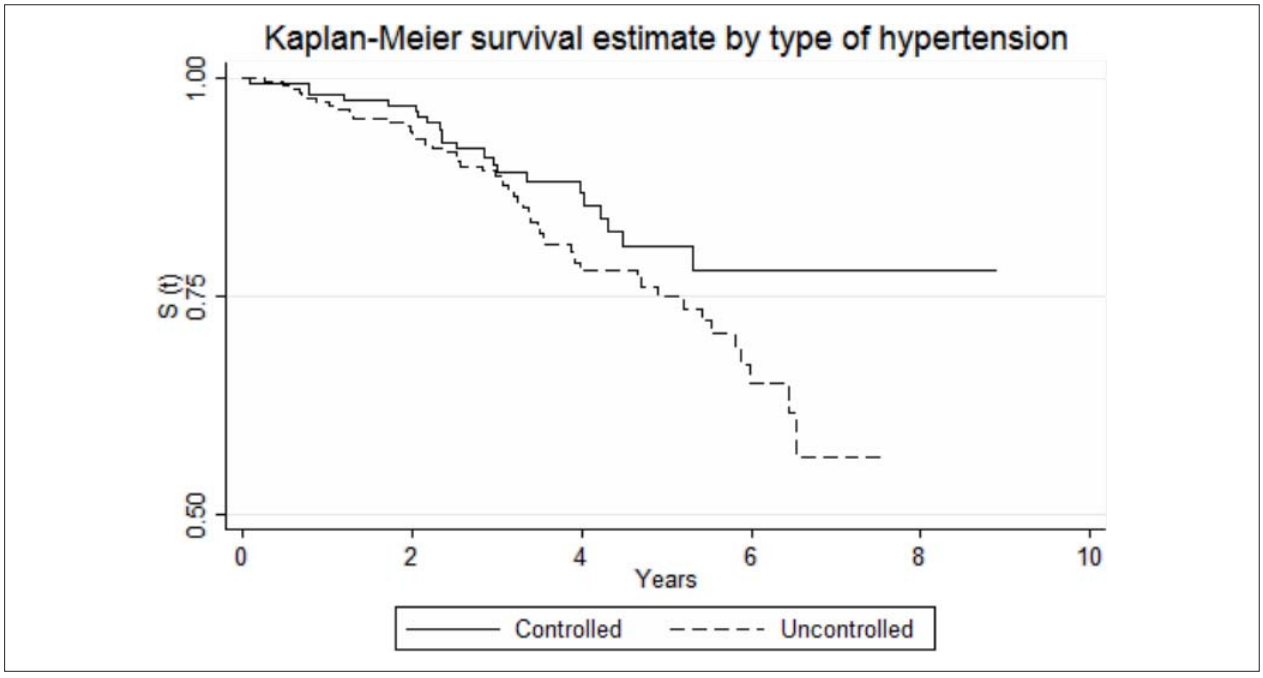

Figure 1 - Probability of event-free survival in women with resistant hypertension grouped as controlled/uncontrolled daytime ABP.

Clement *et al*[11] used a cutoff of 135 mmHg for 24-h systolic BP, and not for daytime BP, as the normal limit for ABP and did not use the diastolic BP. They found a higher risk of cardiovascular events for the patients with mean 24-h systolic BP of 135 mmHg or higher, with an adjusted relative risk (including office BP) of 1.74 (95%CI 1.15-2.48).

Pierdomenico *et al*[12] reported that age, diabetes, previous events and true nonresponsive hypertension (office BP ≥ 140 or 90 mmHg and daytime BP ≥ 135 or 85 mmHg) resulted in independent predictors of outcome in Caucasian patients. The relative risk for true *vs*. false nonresponders (office BP ≥ 140 or 90 mm Hg and daytime BP< 135 or 85 mm Hg) found was 2.33 (95%CI 1.14-4.77).

Verdecchia et al[17] studied subjects diagnosed with essential hypertension and found a strong significant independent association between blunted nocturnal reduction in BP and cardiovascular morbidity in women, but not in men. The association we found was weaker, especially after adjustment for 24-hour BP values, which can suggest that for this population, a higher average BP over the 24 hours explains part of the higher risk in the nondippers.

Hajar *et al*[18] showed that in stroke-free older adults, those with uncontrolled hypertension had an increased risk of incident disability, whereas those with controlled hypertension had a similar risk of incident disability as those without hypertension. They found that, compared with men, women are particularly at an increased risk of developing disability from hypertension. The authors credited the increased predisposition to disability in women to the fact that hypertension is more prevalent among them.

As far as we are concerned, this is the first study focused on resistant hypertensive women. Our results reinforce the need of a more aggressive therapeutic strategy towards blood pressure control in this particular group. Physicians should not downgrade the cardiovascular risk status of women, especially in a high risk population as the one studied here. The role of ABP monitoring to guide therapeutic approaches has been definitely established and the method should be included in the assessment of BP control in resistant hypertensive patients routinely.

Some limitations of our study should be pointed out. There were more losses in the non-controlled group than in the controlled group. This may have produced an underestimated relative risk, so we believe that the differences found could be even bigger without the losses.

Conclusions

This study suggests an association between elevated daytime ABP and cardiovascular risk in resistant hypertensive women. Therefore, to achieve the goal of decreasing cardiovascular morbidity and mortality in this population, the decisions should be based on the control of ABP and not on the control of office blood pressure.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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