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ORIGINAL ARTICLE

Inflammation Markers, Microalbuminuria and Blood Pressure Control in Primary Health Care

Guilherme Brasil Grezzana[1], Bruna Eibel[1], Airton Tetelbom Stein[2], Lúcia Campos Pellanda[1,2]

Instituto de Cardiologia / Fundação Universitária de Cardiologia – IC/FUC[1]; Universidade Federal de Ciências da Saúde de Porto Alegre – UFCSPA / Complexo Hospitalar da Universidade Luterana do Brasil (ULBRA)[2], Canoas, RS – Brazil

Abstract

Background: Systemic arterial hypertension (SAH) is an important cause of cardiovascular morbidity and mortality. In spite of the effectiveness of the treatment, a high number of patients do not obtain blood pressure (BP) control, a fact that implies the need for investigating the role of other additional factors, such as inflammation markers and microalbuminuria, especially in health care environments.

Objectives: To evaluate the association between serum fibrinogen levels, ultra-sensitive C-reactive protein (CRP) and microalbuminuria, with blood pressure (BP) averages evaluated by 24-hour ambulatory blood pressure monitoring (ABPM) in hypertensive patients in primary health care setting.

Methods: A cross-sectional study with hypertensive patients who were seen in primary health care centers was performed. A BP evaluation was carried out by the primary care doctor, and this procedure was followed by a reference test 24-hour ABPM, performed by an independent professional. Moreover, the peripheral blood collect was performed for future biochemical markers analysis.

Results: 143 patients were included. There was a trend for association between the independent variable (altered BP by 24-hour ABPM) and the dependent variable (CRP), there was an association between the values > 3 mg / dL and altered 24-hour ABPM. The prevalence ratio (PR) was of 1.36 (CI 95% 0.90 – 2.06); p=0.18. Regarding microalbuminuria and fibrinogen findings, a 1.03 (CI 95% 0.41 – 2.57) PR was seen; p=1 and 1.19 (CI 95% 0.96 – 1.46) PR; p=0.019, respectively, and both were not significant for altered BP by 24-hour ABPM.

Conclusions: It is a trend for association between CRP with BP evaluated by 24-hour ABPM in the primary care setting. (Int J Cardiovasc Sci. 2016;29(4):295-302)

Keywords: Biomarkers; Inflammation; C-Reactive Protein; Albuminuria; Blood Pressure Monitoring, Ambulatory.

Introduction

Even though the relation between high cardiovascular risk and arterial hypertension is well defined, there are few patients who adhere to high blood pressure (BP) medication, and the proportion of them who have the BP controlled is even smaller.[1] In Brazil, 39% of hypertensive patients have their BP controlled (< 140 / 90 mHg) at primary health care level, and 33% of these patients were classified as stages 2 or 3 of hypertension (BP > 160 / 110 mmHg).[2]

Microalbuminuria in hypertension has been observed as an important predictor of renal damage and cardiovascular disease.[3] Hypertensive patients with baseline microalbuminuria have a 55% higher risk for cardiovascular outcomes in a follow up period of 5 years.[4] Thus, the evaluation of albuminuria in Cardiovascular Disease (CVD) has been recommended by international clinical guidelines.[5]

Fibrinogen is an inflammatory marker that is related to the increase of frequency in vascular events,[6] which reflects a state of hypercoagulation and contributes to the

Mailing Address: Guilherme Brasil Grezzana
Instituto de Cardiologia / Fundação Universitária de Cardiologia
Avenida Princesa Isabel, 370, 3º andar. Postal Code: 99620-000, Porto Alegre, RS – Brazil
E-mail: gbgrezzana@yahoo.com.br

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progression of atherosclerosis.[7] There is an association between high levels of fibrinogen and essential hypertension,[8] risk of coronary heart disease (CHD) and mortality by stroke.[7] The literature also describes an association between hypertension and CRP.[9]

Although the association between inflammation, microalbuminuria and hypertension has been evaluated, the use of these markers together and the evaluation of blood pressure in 24 hours is not a routine in primary health care centers, being used more commonly in patients at high cardiovascular risk.[5] The objective of the present study was to evaluate the association between inflammatory markers, microalbuminuria and hypertension, which was evaluated through 24-hour ABPM in primary health care centers.

Methods

Participants

A cross-sectional study was carried out in Antonio Prado (RS), a town in southern Brazil. The inclusion criteria were: hypertensive patients who sought care in the public primary health care from January 2009 through December 2010, were 18 years old or older, who had been taking anti-hypertension medication in the last three months to present the stable signals in accordance with the condition. Also, the patients needed to be able to answer the study's questionnaire. The exclusion criteria were: patients who were not able to answer the questionnaire and those who lived outside the area covered by the local health centers, pregnant women, individuals who presented electrocardiograms with non-sinus rhythm and infectious or inflammatory disease.

The sample size required to evaluate the accuracy between the two methods of BP measurement, we assumed a probability of 30% for ABPM and 10% for the BP measurement by primary health care doctors. The confidence interval was 95% and the power was 80%. The estimated sample size was 142 patients. Antônio Prado (RS) is a town in Southern Brazil that has 12,837 inhabitants,[10] which has two primary health care units; therefore, the sample of 143 hypertensive patients represent those that sought care in both units at period of this study.

All participants signed the agreement term to participate in the study. The project was approved by the institutional review board (IC/FUC – 4278.08).

Biochemical and Anthropometric Parameters

For the microalbuminuria measurements, the urine sample was obtained in the morning period by a single sample through the nephelometric method for protein dosage.[11] The urine sample was processed in the same day, and an evaluation of microalbuminuria and creatinine was performed. Microalbuminuria was defined as higher than 30 mg/g and lower than 300 mg/g creatinine, considering the rate of albumin to creatinine.

Furthermore, the peripheral blood collect was performed early in the morning during fasting for analysis of biochemical markers: fibrinogen, total cholesterol, HDL, triglyceride, LDL, creatinine, potassium, CRP, complete blood count, glycated hemoglobin A1c and glycaemia. We considered rates above 400 mg/dL abnormal to fibrinogen (Clauss assay), and rates above 3 mg/dL abnormal to CRP.

Additionally, weight, height, body mass index, waist-hip ratio and the habit of smoking and/or consuming alcohol were evaluated.[12]

Conventional measurement of BP and ABPM

The primary health doctors performed three BP measurements using a mercury sphygmomanometer and an appropriate sized cuff, with the patient sitting and after 5 minutes of rest. The method of BP measurement was in accordance with the European Society of Cardiology.[13] The patient had answered a questionnaire and a 12-lead electrocardiogram and the application of the ABPM were performed. The ABPM was applied during a regular working day of the patients and the results of the BP measurement by the doctors were blinded.

ABP monitors were validated in accordance with the British Society of Hypertension.[14] The ABPM recorder used in this study was DMS Brasil, version TM2430, and the mercury sphygmomanometer was MDF 800. The measurements of the 24-hour ABPM were performed every fifteen minutes during the period of wakefulness and every thirty minutes during the period of sleep, and they were adjusted to match the patients' usual time to go to sleep and wake up. Data originated from a minimum of 70 records throughout 24 hours, with at least two records every hour during the night, were considered adequate. The parameters evaluated by the ABPM were: average systolic and diastolic BP in 24 hours, systolic and diastolic BP during the period of wakefulness and during the night. Hypertension through conventional measurements with the use of sphygmomanometer

was defined as having a value equal to or higher than 140/90 mmHg. The ABPM criterion for non-controlled hypertension was the average 24-hour BP values above 130/80 mmHg. Regarding the values related to the period of wakefulness, non-controlled BP was considered as an average above 130/80 mmHg. The absence of nocturnal dipping was defined as a reduction of BP by ABPM inferior or equal to 10% in relation to the diurnal average. Current clinical guidelines do not present clear cut-off values for criteria of definition of normality for 24-hour BP, thus, the same values between diabetics and non-diabetics were considered.

Statistical Methods

The data were analyzed in the statistical program SPSS 17.0. We performed descriptive statistics with continuous (mean and standard deviation) and categorical variables. In order to evaluate the association between the measurements of fibrinogen, microalbuminuria and BP values (based on the ABPM), a Chi-squared test, a Fisher's test and, a logistic regression with controlled and non-controlled ABPM as a dependent variable were performed. A statistically significance was defined as $p < 0.05$.

Results

Between January 2009 and December 2010, 146 hypertensive patients were included. Three patients were excluded, as they did not follow the protocol. The main antihypertensive drug classes used were angiotensin-converting-enzyme inhibitor, thiazide diuretics and beta-blockers. The characteristic of the sample is described on Table 1 – women (67%), white (79.6%), age of 59.8 years old (SD 12.74), 21% with diabetes, 63.6% presented high cholesterol level, 9.2% were smokers, 16.1% drink regularly and 32.6% were obese. When evaluating the fibrinogen results above 400 mg/dL and 24-hour ABPM alteration, a PR of 1,19 (CI 95% 0.96 - 1.46); p=0.019, was found. When CRP was considered, the association between values > 3 mg/dL and higher of BP that is considered altered in 24-hour ABPM, a PR of 1.36 (CI 95% 0.90 - 2,06); p=0.18, was observed. The association between microalbuminuria (30 mg/g to 300 mg/g) and higher BP that is considered altered in 24-hour ABPM showed a PR 1.03 (CI 95% 0.41 - 2.57); p=1 (Table 2). The male variable was 1.37 times more likely to change in ABPM compared to the female gender. A logistic regression was performed for each of the variables (CRP, fibrinogen, and microalbuminuria) adjusted for gender, age, DM, BMI in relation to the non-controlled ABPM, with findings on microalbuminuria (p=0.98), CRP (p=0.074) and fibrinogen (p=0.304) not significant.

Discussion

This study has shown a trend of association between inflammatory marker CRP and non-controlled BP that is considered altered in 24-hour ABPM in hypertensive patients in primary healthcare, although microalbuminuria and fibrinogen were not associated. The results obtained through the utilization of 24-hour ABPM showed 44.8% of non-controlled hypertensive patients (>130/80 mmHg), 72% with absence of nocturnal dipping of BP, and 41.9% without BP control during the wakefulness period (Table 3). These findings suggest that, when a more accurate method for BP evaluation is used, such as the 24-hour ABPM, a large number of hypertensive patients who are assisted in ambulatories of primary healthcare units remain with non-controlled BP, despite the anti-hypertension treatment that is adopted.

High levels of CRP in hypertensive patients are probably caused by a reduction in the production of nitric oxide in endothelial cells and, consequently, by arterial vasoconstriction, thus indicating a correlation between endothelial dysfunction and the renin-angiotensin system[9]. Moreover, prospective studies showed an association between inflammation and an increase in the risk of events of cardiovascular mortality, as well as the fact that chronic inflammatory condition can be an independent risk factor for SAH.[15] In the present study, we observed a correlation trend between CRP values > 3 mg/dL and alteration in 24-hour ABPM. Also, out of the 86 (60.1%) patients who had blood pressure above 130/80 mmHg, 68 patients (61.8%) presented CRP values above 1 mg/dL. This finding is consistent with the results of epidemiological studies that correlated latent inflammatory state and hypertension.[16,17]

The 24-hour ambulatory blood pressure monitoring (ABPM) has several advantages besides being the reference test for cardiovascular outcome.[18] ABPM allows an evaluation of the pattern of nocturnal BP and its relation to the damage of target organs. It also helps diagnose white coat hypertension and masked hypertension.[19,20] From the 86 (60.1%) patients who had blood pressure above 130/80 mmHg, 30 patients (69.8%) presented fibrinogen above 400 mg/dL. Plasmatic

Table 1
Descriptive characteristics of the sample

Variables	Frequency in percentage and average
Demographic variables	
N	143
Sex, Female	96 (67%)
Age	59.8 (29 – 89)
White	113 (79.6%)
Diabetic	30 (21%)
Inflammatory markers	
Hs-CRP > 3 (mg/dL)	59 (41.3%)
Fibrinogen > 400 (mg/dL)	42 (29.37%)
Metabolic descriptors	
Glycated hemoglobin A1C	6.19 (4.4 – 13.14)
Glucose fasting, (mg/dL)	101 (53 – 282)
Microalbuminuria (mg/g creatinine)	91.9 (1.3 – 3471)
Lipid variables	
Total cholesterol, (mg/dL)	212.55 (125 – 362)
HDL, (mg/dL)	49.15 (22 – 91)
LDL, (mg/dL)	130.7 (55 – 265)
Triglycerides, (mg/dL)	164.13 (50 – 626)
Anthropometric data	
BMI, Kg/m^2	27.98 (19.8 – 47.9)
Normal	30.5%
Overweight	36.9%
Obesity	32.6%
Waist/Hip	1.52
Lifestyle	
Smokers	13 (9.2%)
Alcohol use > 5 drinks per day	23 (16.1%)

fibrinogen is a major determinant of plasma viscosity and its high levels may be associated with risk of stroke.[7] This same study describes a correlation between high plasmatic fibrinogen and BP evaluated through 24-hour ABPM, which contributes to the prognosis of silent cerebrovascular lesions. In another study[21], the correlation between masked hypertension and high serum levels of fibrinogen was observed, in comparison with normotensive controls. This is an important finding for the follow-up of hypertensive patients, since, in our study, we had 12.58% of patients who presented controlled BP in the doctor's office, but showed altered BP in the 24-hour ABPM. Moreover, plasmatic fibrinogen is a risk factor for CHD and peripheral vascular disease.[8] The utilization of inflammatory markers such as the fibrinogen dosage and CRP in hypertensive patients in primary health care center may help detect patients with an inadequate control of BP.

Table 2
Analysis bivariate between non-controlled ABPM and study's variables

Variables	ABPM controlled*	Altered ABPM** N 143	p value
Sex, male	19 (44.2%)	28 (59.6%)	0.021
Diabetic	57 (45.2%)	7 (41.2%)	0.955
Inflammatory markers			
Hs-CRP > 3 (mg/dL)***	37 (62.7%)	22 (37.3%)	0.18
Fibrinogen > 400 (mg/dL)	19 (44.2%)	24 (55.8%)	0.019
Metabolic descriptors			
Microalbuminuria > 30 (mg/g creatinine)	12 (54.5%)	10 (45.5%)	1

* < 130/80 mmHg; ** > 130/80 mmHg; *** Ultra-sensitive C-reactive protein

Table 3
BP measurements using ABPM taken in a medical office

ABPM	Frequency in percentage and average
Systolic 24 hour (mmHg)	128 (96 – 166)
Diastolic 24 hour (mmHg)	75.8 (58 – 99)
Dipper	40 (28%)
Non-dipper	103 (72%)
Office measurements	
Systolic (mmHg)	143.69 (90 – 220)
Diastolic (mmHg)	85.83 (60 – 120)

The evaluation of microalbuminuria is a prognostic marker of cardiovascular and renal risk for both diabetic and non-diabetic patients;[22] therefore, it is recommended for the follow-up of hypertensive patients in pharmacological treatment.[12] In the LIFE study,[23] after a year of anti-hypertensive treatment, microalbuminuria was more important as a predictor for cardiovascular outcome than Framingham Risk Score. In the Ontarget-Transcend study,[24] mortality rates were higher in patients with albuminuria (RR 1.56) and lower in patients with a decrease in urinary albumin (RR 0.84). However, the findings of our study were not significant (p=1) when we compared the results for microalbuminuria and non-controlled BP by 24-hour ABPM. These findings are probably related to the size of the sample and/or the variability in the analysis time of the urinary samples. The collection of samples should ideally be performed in at least two samples, which would be obtained with an interval between them. Nonetheless, the findings of the ADVANCE study[25] showed that the increase or reduction of the cardiovascular risk is independent from the systolic and diastolic BP values when microalbuminuria is utilized. Thus, it reinforces the requirement of microalbuminuria for hypertensive patients in primary health care settings.

At bivariate analysis, men were 1.37 times more likely to change in the 24-hour ABPM if compared to women

(p=0.021). However, when a multivariate analysis for CRP (p=0.074) , microalbuminuria (p=0.98) and fibrinogen (p=0.304) was performed, adjusted for sex, age, DM and BMI, no biochemical marker was significant as a predictor to control 24-hour ABPM.

A limitation of the current study was BP measurement only one time through the 24-hour ABPM, which could have an effect on reproducibility of the measurements, especially when the nocturnal period of BP evaluation is considered. As the sleeping and wakefulness were set individually for each patient, there might be risk of bias, although it was carried out this way in order to present the real characteristics of the living condition. The sample had included every hypertension patient in the town and it could be regarded as a population-based study. This epidemiology survey demonstrated a health technology assessment through biochemical analysis and BP measurement and, it is essential to have the whole spectrum of hypertensive patients in primary health care centers. We believe that with a larger sample size the association between inflammatory markers and alteration in 24-hour ABPM would be more evident.

Conclusions

The results of our study highlights the importance of using complementary diagnostic tools in order to reach a more comprehensive diagnosis for hypertension in primary health care setting. The accuracy in BP measure increased when the biochemical profile of patients was carried out. Thus, although this study demonstrated that the adjusted variables were not significant for non-controlled BP by ABPM, it suggests that the utilization of biochemical markers may have contributed to the confirmation of accuracy diagnostic to non-controlled hypertension through the 24-hour ABPM. The use of inflammatory biochemical markers may contribute to the diagnosis of non-controlled BP in primary health care should be recommended.

Author contributions

Conception and design of the research: Grezzana GB, Eibel B, Stein AT, Pellanda LC. Acquisition of data: Grezzana GB. Analysis and interpretation of the data: Grezzana GB, Eibel B,Stein AT, Pellanda LC. Statistical analysis: Grezzana GB, Eibel B, Stein AT, Pellanda LC. Obtaining financing: Grezzana GB. Writing of the manuscript: Grezzana GB, Eibel B, Stein AT, Pellanda LC. Critical revision of the manuscript for intellectual content: Grezzana GB, Eibel B, Stein AT, Pellanda LC.

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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