International Journal of Cardiology 203 (2016) 98–103

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Office blood pressure is a predictor of aortic elastic properties and urinary protein excretion in subjects with white coat hypertension☆

Konstantinos Aznaouridis *, Charalambos Vlachopoulos, Konstantina Masoura, Panagiota Pietri, Gregory Vyssoulis, Nikolaos Ioakeimidis, Christodoulos Stefanadis, Dimitrios Tousoulis

Hypertension Unit, 1st Department of Cardiology, Athens Medical School, Hippokration Hospital, Athens, Greece

ARTICLE INFO

Article history:
Received 4 July 2015
Received in revised form 16 September 2015
Accepted 12 October 2015
Available online 22 October 2015

Keywords:
α1-Microglobulin
Albuminuria
Aortic stiffness
Pulse wave velocity
Wave reflections
White coat hypertension

ABSTRACT

Background: White coat hypertension (WCH) is related to target organ damage and increased cardiovascular risk. Arterial elastic properties and urinary protein excretion are determinants of cardiovascular performance and predictors of outcomes. We investigated whether office blood pressure (BP) is a better determinant of arterial and renal function than the ambulatory BP in WCH patients.

Methods: We studied 440 consecutive untreated non-diabetic patients with WCH (office BP >140/90 mm Hg, mean daytime ambulatory BP <135/85 mm Hg). Arterial function was evaluated with carotid–femoral pulse wave velocity (cfPWV), an index of aortic stiffness, and aortic augmentation index (AIx), a composite marker of aortic stiffness and wave reflections. In 24-hour urine, albumin excretion and albumin/creatinine ratio (ACR) were measured as markers of glomerular function and urinary α_1-microglobulin was measured as a marker of renal tubular function.

Results: In univariate analysis, office systolic BP correlated significantly with cfPWV ($r = 0.245$, $P < 0.001$), AIx ($r = 0.31$, $P < 0.001$), albumin ($r = 0.134$, $P = 0.005$), ACR ($r = 0.199$, $P < 0.001$) and α_1-microglobulin ($r = 0.118$, $P = 0.013$). In contrast, mean ambulatory systolic BP did not correlate with arterial function or urinary proteins (all $P > 0.5$). Hierarchical multilevel linear regression analysis showed that office systolic BP is an independent determinant of cfPWV ($P = 0.050$), AIx ($P = 0.029$), albumin ($P = 0.002$) and ACR ($P = 0.001$) and has a borderline association with α_1-microglobulin ($P = 0.088$).

Conclusions: In non-diabetic WCH individuals, office systolic BP is an independent predictor of aortic elastic properties and urinary protein excretion, whereas ambulatory BP is not. This finding suggests that office BP may be a marker of cardiovascular risk in subjects with WCH.

1. Introduction

White coat hypertension (WCH) is defined as the occurrence of persistently elevated office blood pressure (BP) in patients with normal ambulatory daytime BP. WCH is a common phenotype with a prevalence of approximately 15% in the general population [1]. Several studies suggest that WCH is not an entirely innocent phenotype. Individuals with WCH have greater left ventricular mass compared to normotensives [2,3] and they are more likely to develop sustained hypertension [2,4] and diabetes [5].

Although a recent meta-analysis reported that the risk of cardiovascular events is not significantly higher in WCH patients compared to normotensive subjects, these findings were confounded by the substantially higher rate of antihypertensive medications in WCH groups [6]. Importantly, longitudinal studies have documented that WCH is associated with increased cardiovascular risk [4,7,8], as the incidence of cardiovascular events is intermediate between sustained hypertension and normotension [4,7].

Arterial elastic properties, such as aortic stiffness and wave reflections, are important determinants of cardiovascular performance and independent predictors of outcomes in several populations, including patients with sustained hypertension [9–15]. Similarly, the levels of proteins excreted in the urine have been associated with cardiovascular events. Microalbuminuria is an established independent predictor of mortality risk both in the general population [16] and in hypertensive patients [17], whereas high urinary excretion of α1-microglobulin (α1-MG), a marker of renal tubular dysfunction, correlates with increased cardiovascular risk in non-diabetic hypertensive patients [17].

Ambulatory BP is a better predictor of hypertension-related cardiovascular outcomes than office BP [18,19]. However, existing evidence supports that WCH is likely associated with increased cardiovascular risk [4,7,8], despite that WCH patients have ambulatory BP within normal range. Therefore, we sought to investigate whether office BP,

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Kyparissias 14, Kato Acharnes, Athens 13671, Greece.
E-mail address: conazna@yahoo.com (K. Aznaouridis).

http://dx.doi.org/10.1016/j.ijcard.2015.10.078
0167-5273/

which is by definition abnormal in WCH, is related to target organ damage. In the present study, we hypothesized that the office BP is a better determinant of arterial function and protein excretion in the urine than the ambulatory BP in patients with WCH.

2. Methods

2.1. Study population

In this observational, single-center, cross-sectional, retrospective study, we enrolled patients who had been referred to the Hypertension Unit of our Department between February 2003 and February 2009 for evaluation of hypertension and were eventually diagnosed with WCH. The enrolled subjects were not taking any antihypertensive medication. Before enrollment, a full medical history was taken and physical examination was performed. Patients with diabetes, renal impairment (serum creatinine > 1.5 mg/dl), acute or chronic inflammatory diseases, endocrinopathies, history of cerebrovascular event, heart failure, coronary artery disease, or severe obesity (body-mass index > 36 kg/m^2) were excluded from the study. Subjects who were taking regular cardiovascular medications, antioxidant vitamin supplementation, anti-inflammatory or steroid substances, or female participants on oral contraceptives were also excluded. Weight and height were measured in all subjects and body mass index was calculated. Current smokers were defined as those who smoked at least one cigarette per day. The study finally included 440 untreated non-diabetic subjects with WCH. All participants gave their informed consent to participate in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the local Ethics Committee.

2.2. BP measurements and diagnosis of WCH

Office BP was measured in a sitting position with mercury sphygmomanometry after a 5-min rest, in two different visits a week apart. The measurements were obtained between 9 and 11 am. In every visit, systolic and diastolic BP were measured. The first and the fifth phase of the Korotkoff sounds were used to identify the systolic BP and diastolic BP respectively. Three readings one minute apart were performed, and the mean value of both visits (a total of 6 measurements) was calculated.

Twenty-four hour BP measurements were carried out with a commercially available portable noninvasive ambulatory BP recorder (SpaceLabs 90207, Redmond, WA, USA). The recorder was calibrated with a mercury column and was set to take readings at 15-min intervals from 6:00 AM to 10:00 PM, and every 30 min from 10:00 PM to 6:00 AM. All subjects were encouraged to carry out their normal daily routine after they left the hospital. All readings were played back on Q standard replay unit (SpaceLabs) and analyzed on a PC.

WCH was defined as office BP >140/90 mm Hg and mean daytime ambulatory BP <135/85 mm Hg [6,19].

2.3. Evaluation of aortic elastic properties

All measurements were conducted in the morning between 9 and 11 am, with the individual in a supine position, in a quiet environment. Participants were requested to abstain from tobacco, coffee and food at least 5 h and from alcohol 12 h before the examination.

Carotid–femoral pulse wave velocity (cfPWV), an established index of aortic stiffness [9–12,15] and carotid–radial pulse wave velocity (crPWV), a measure of medium-sized (muscular) artery stiffness, were obtained using a validated non-invasive device (Complior, Artech Medical, Pantin, France), which allows online pulse wave recording and automatic calculation of pulse wave velocity. The PWV was calculated from measurements of pulse transit time and the distance traveled between two recording sites (pulse wave velocity = distance [meters] / transit time [seconds]). Three different pressure waveforms were obtained at three sites: the right carotid, radial and femoral artery. The time delay between the feet of the recorded proximal (carotid) and distal waves (femoral and radial) was automatically calculated. For the calculation cfPWV, the distance was estimated by subtracting the distance between the carotid location and the sternal notch from the distance between the sternal notch and the femoral site. For the calculation of crPWV, the distance was estimated by subtracting the distance between the carotid location to the sternal notch from the distance between the carotid location and the radial site. The mean PWV of at least 10 consecutive pressure waveforms was calculated for further analysis.

Augmentation index (AIx) was measured as a composite measure of the magnitude of wave reflection and arterial stiffness, which affects timing of wave reflections [14]. Augmented pressure is the pressure added to the incident wave by the returning reflected wave and represents the increased afterload that left ventricle must cope with. AIx is defined as augmented pressure divided by central pulse pressure and is expressed as a percentage. The peripheral pulse wave was recorded from the radial artery using the method of applanation tonometry, and was subsequently transformed into the central pulse wave of the aorta through pulse wave analysis with the SphygmoCor device (AtCor Medical, Sydney, Australia). AIx was averaged from ten to twelve successive waves and was corrected for a steady heart rate of 75 bpm.

2.4. Evaluation of renal function and urinary protein excretion

The estimated glomerular filtration rate was calculated with the Modification of Diet in Renal Disease Study (MDRD) equation. The 24-h urine was collected after the patients had received detailed instructions and was used to determine urinary excretion of albumin, creatinine and α1-MG. The concentrations of albumin and α1-MG in urine were measured with immuno-nephelometry (BN system; Dade-Behring Marburg GmbH). 24-h urine excretion of albumin and α1-MG was expressed as total excretion in 24 h. The albumin/creatinine ratio (ACR) was calculated as the ratio of total excreted albumin (in milligrams) to total excreted creatinine (in grams) in the 24-h urine.

2.5. Statistical analysis

Continuous variables are expressed as mean value ± standard deviation (SD), while categorical variables are presented as absolute or relative frequencies. For continuous variables, the assumption of normality was tested using the Kolmogorov–Smirnov criterion and with visual inspection of the distribution histograms. Logarithmic transformation was performed for distributions that were significantly skewed before analysis (albumin and ACR). Skewed variables had a remarkably good fit to normal distribution after log transformation, and they are expressed as median value (25th–75th percentile). Correlations between variables were evaluated by calculation of the Pearson correlation coefficient. Comparisons of arterial function indices and 24 h urinary proteins among quartiles of BP (shown in figures) were performed using one-way analysis of variance (ANOVA). Hierarchical multilevel multiple linear regression analysis was performed to estimate the adjusted effects of office systolic BP or mean ambulatory daytime systolic BP on arterial function (cfPWV and AIx) or 24 h urinary proteins (albumin, ACR, α1-MG). All potential confounders were entered as covariates (age, gender, smoking, body-mass index, HbA1c). Separate models for office systolic BP and mean ambulatory daytime systolic BP were constructed. All covariates were retained in each final model. Exact P values < 0.05, were considered statistically significant. Data analysis was performed with SPSS software, version 13.0 (Chicago, IL).

3. Results

We studied 440 untreated non-diabetic patients with WCH (172 men, 268 women, age 52.5 ± 12.3 years). The characteristics of the study population are shown in Table 1.

In univariate analysis, office systolic BP had a statistically significant but rather weak correlation with daytime systolic BP ($r = 0.15$, $P = 0.001$). Office systolic BP correlated significantly with cfPWV ($r = 0.245$, $P < 0.001$) and AIx ($r = 0.31$, $P < 0.001$), but no with crPWV ($r = -0.049$, P = NS). Furthermore, office systolic BP also correlated significantly with eGFR ($r = -0.252$, $P < 0.001$), 24 h urine albumin ($r = 0.139$, $P = 0.014$), ACR ($r = 0.221$, $P < 0.001$) and α_1-MG ($r = 0.118$, $P = 0.013$). In contrast, mean daytime ambulatory systolic BP

Table 1
Characteristics of the study population.

Age (years)	52.5 ± 12.3
Gender (males/females)	172/268
Smoking (%)	36
BMI (kg/m^2)	27.1 ± 4.0
Office systolic pressure (mm Hg)	158 ± 9
Office diastolic pressure (mm Hg)	98 ± 7
Office pulse pressure (mm Hg)	60 ± 12
Daytime ambulatory systolic pressure (mm Hg)	124 ± 7
Night ambulatory systolic pressure (mm Hg)	110 ± 10
Daytime ambulatory diastolic pressure (mm Hg)	77 ± 5
Night ambulatory diastolic pressure (mm Hg)	66 ± 7
Serum creatinine (mg/dl)	0.91 ± 0.17
eGFR (ml/min/1.73 m^2)	81.7 ± 20.3
Glycated hemoglobin (%)	5.4 ± 0.5
cfPWV (m/s)	7.1 ± 1.2
crPWV (m/s)	8.1 ± 1.1
AP (mm Hg)	12.4 ± 7.4
AIx (%)	23.4 ± 11.9
24 h urine albumin (mg/24 h)	10.3 (7.2–14.8)
24 h urine ACR (mg/g)	13.2 (7.7–20.2)
24 h urine α1-microglobulin (mg/24 h)	4.8 ± 1.9

Categorical variables are presented as absolute or relative frequencies, while continuous variables as mean value ± SD for normally distributed and median value (25th–75th percentile) for skewed variables.
ACR indicates albumin/creatinine ratio; AIx augmentation index; AP, augmented pressure; BMI, body-mass index; cfPWV carotid–femoral pulse wave velocity; crPWV carotid–radial pulse wave velocity, eGFR estimated glomerular filtration rate.