Original Article

C-Reactive Protein and B-Type Natriuretic Peptides in Never-Treated White Coat Hypertensives

David CONEN^{1),2),*}, Thomas DIETERLE^{2),*}, Katrin UTECH¹⁾,
Miriam RIMNER¹⁾, and Benedict MARTINA¹⁾

Arterial hypertension has been associated with increased plasma concentrations of C-reactive protein (CRP) and B-type natriuretic peptide (BNP). This study tested the hypothesis that patients with white coat hypertension have lower plasma CRP and BNP concentrations than those with sustained hypertension. A total of 109 consecutive medical outpatients with never-treated office hypertension underwent ambulatory blood pressure monitoring and blood sampling to determine CRP and BNP concentrations. Patients with treated hypertension, lipid-lowering therapy, renal insufficiency or structural heart disease other than left ventricular hypertrophy were excluded. White coat hypertension was defined as office hypertension associated with mean daytime blood pressure values below 135/85 mmHg. A control group of 48 consecutive, age- and sex-matched patients without office hypertension were recruited during the same period. Twenty-six patients (24%) had white coat hypertension. There were no statistically significant differences in baseline variables between patients with sustained hypertension and white coat hypertensives, except for mean blood pressure values. Mean CRP was 3.2 ± 5.1 mg/l in patients with white coat hypertension compared to 3.4 ± 4.2 mg/l in those with sustained hypertension ($p=0.79$). Control patients had significantly lower CRP values than patients with either white coat or sustained hypertension (1.2 ± 0.9 mg/l, $p=0.002$ and $p=0.038$, respectively). Mean BNP concentrations were 21 ± 25 pg/l and 44 ± 125 pg/l in white coat and sustained hypertensives, respectively ($p=0.36$). The plasma concentrations of CRP and BNP did not differ between patients with white coat hypertension and those with sustained hypertension. (*Hypertens Res* 2006; 29: 411–415)

Key Words: C-reactive protein, hypertension, B-type natriuretic peptide, ambulatory blood pressure monitoring, inflammation

Introduction

Current evidence supports a central role of inflammation in the development of arteriosclerosis (1). Arterial hypertension, a leading cardiovascular risk factor, has been associated with increased plasma concentrations of C-reactive protein (CRP), a marker of systemic inflammation (2–4). Even in patients with high normal blood pressure inflammatory markers are increased, when compared to a normotensive population (5). In some subtypes of hypertension, inflammatory markers are

still higher (6). CRP and blood pressure are independent determinants of cardiovascular risk in hypertensive patients, and their predictive value is additive (7). Furthermore, an increased CRP concentration is an independent risk factor for the development of hypertension in previously normotensive individuals (8).

White coat hypertension is defined as blood pressure values higher than normal in the medical environment, but normal blood pressure values when pursuing usual daily activities (9). Individuals with white coat hypertension are at lower risk for cardiovascular events or target organ damage than patients

From the ¹⁾Medical Outpatient Clinic and ²⁾Department of Cardiology, University Hospital Basel, Basel, Switzerland.

*These authors contributed equally to the present article.

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Address for Reprints: David Conen, M.D., University Hospital, Petersgraben 4, 4031 Basel, Switzerland. E-mail: Conend@uhbs.ch

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Table 1. Baseline Clinical and Biological Characteristics among Patients with Definite or White Coat Hypertension and Control Patients

	Hypertensive patients (n=109)	Definite hypertension (n=83)	White coat hypertension (n=26)	Control patients (n=48)
Age (years)	53±13	54±12	51±16	52±15
Men (%)	65 (60)	47 (57)	18 (69)	22 (46)
BMI (kg/m ²)*	27.5±5	27.2±5	28.7±4	25.6±5 [†]
Office SBP (mmHg)	158±13	161±14	151±10 [‡]	122±12 [§]
Office DBP (mmHg)	96±7	97±7	92±6 [‡]	74±9 [§]
Ambulatory SBP (mmHg)	141±14	146±11	125±7	—
Ambulatory DBP (mmHg)	89±9	92±8	78±6	—
Left ventricular mass index (g/m ²)	94±37	94±37	95±34	—
Left ventricular hypertrophy (%)	17	16	20	—
E/A ratio	1.0±0.4	1.1±0.3	1.0±0.3	—
Total cholesterol (mmol/l)	5.55±1.14	5.60±1.12	5.37±1.20	5.24±1.09
HDL cholesterol (mmol/l)	1.44±0.48	1.47±0.50	1.34±0.38	1.59±0.41 [¶]
LDL cholesterol (mmol/l)	3.29±0.95	3.30±0.94	3.24±1.01	3.00±0.88
Triglycerides (mmol/l)	1.82±1.08	1.83±1.16	1.76±0.78	1.38±0.87 ^{**}
Creatinine (μmol/l)	73±15	72±15	76±15	75±13
hsCRP (mg/l)	3.4±4.4	3.4±4.2	3.2±5.1	1.2±0.9 ^{***}
BNP (pg/ml)	38±110	44±125	21±25	—

Data are number of patients (%) or mean±SD. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hsCRP, high sensitivity C-reactive protein; BNP, B-type natriuretic peptide. *Weight divided by squared height. [†] $p=0.007$ vs. patients with white coat hypertension. [‡] $p=0.001$ vs. patients with definite hypertension. [§] $p<0.001$ vs. patients with definite and patients with white coat hypertension. ^{||} $p<0.001$ vs. patients with definite hypertension. [¶] $p=0.032$ vs. patients with white coat hypertension. ^{**} $p=0.016$ vs. patients with definite hypertension. ^{***} $p=0.002$ vs. patients with definite hypertension and $p=0.038$ vs. patients with white coat hypertension.

with sustained or definite hypertension (10). However, little data is available on biomarker concentrations in patients with white coat hypertension. In a subgroup analysis of Schillaci *et al.*, CRP concentrations in white coat hypertensives were found to be similar to those in control patients (3).

B-type natriuretic peptide (BNP) is a hormone released primarily by the ventricles in response to volume overload, increased filling pressures or myocardial stretch. It has been shown that BNP levels are increased in patients with hypertension compared to the general population (11), and that elevated BNP levels in the general population are associated with a higher number of cardiovascular events (12). To our knowledge, there has been a lack of studies examining BNP concentrations in patients with white coat hypertension.

Based on these findings, the goal of this study was to prospectively test whether patients with white coat hypertension have lower plasma CRP and BNP concentrations than those with sustained hypertension.

Methods

Study Population

Between August 2003 and August 2004, 1,500 consecutive adult general medical outpatients were screened for office

hypertension when entering the Medical Outpatient Clinic of the University Hospital Basel, Switzerland. Blood pressure was measured in a quiet environment and in a sitting position after at least 5 min of rest, according to the current guidelines (13). Elevated office blood pressure was defined as a mean of two blood pressure measurements $\geq 140/90$ mmHg at two different consultations. All patients with elevated office blood pressure were asked to participate in the study. Patients with treated hypertension, missing informed consent, clinical or echocardiographic signs of depressed left ventricular function (ejection fraction $<45\%$) or significant valvular heart disease, secondary causes of hypertension, coronary artery disease, previous stroke, peripheral artery disease, renal insufficiency (creatinine >130 μmol/l) or any other severe concomitant disease were excluded.

Age- and sex-matched non-hypertensive subjects served as control patients. Control patients were retrospectively recruited from the same outpatient population as hypertensive patients. Baseline characteristics, blood lipids and CRP values were abstracted from patient charts. Patients with malignancies, inflammatory disorders, overt arteriosclerotic disease and acute infections were excluded. BNP concentrations were not available for control patients.

The study was approved by the local ethics committee. Written informed consent was obtained for hypertensive

Fig. 1. Distribution of CRP levels in patients with definite or white coat hypertension and control patients. HT, hypertension; CRP, C-reactive protein.

patients and the study complied with the Declaration of Helsinki.

Procedures

Ambulatory blood pressure measurements were performed with validated devices (Mobilograph, Stolberg, Germany). The devices were set to take a reading every 20 min during the daytime and every 40 min during the nighttime. The patients were told to pursue normal daily activities and to hold their non-dominant arm relaxed during measurements. We considered as invalid any values of systolic blood pressure <50 mmHg or >250 mmHg, or diastolic blood pressure <30 mmHg or >150 mmHg. White coat hypertension was defined as office blood pressure $\geq 140/90$ mmHg and average daytime blood pressure <135/85 mmHg.

Non-fasting venous blood samples were collected in EDTA-containing tubes and processed immediately. CRP was assayed by immunoturbidimetry (Hitachi, Roche, Switzerland). BNP concentrations were determined by immunofluorescence (AxSYM®; Abbott Laboratories, Abbott Park, USA). The detection limits for CRP and BNP in our laboratory were 0.5 mg/l and 10 pg/ml, respectively. Concentrations of BNP and CRP below these limits were assigned a value of 0.25 mg/l and 5 pg/ml, respectively.

Echocardiography was performed in 100 of 109 patients (92%) with hypertension using a Hewlett Packard 5500 system (Hewlett Packard, Andover, USA). Control patients did not have echocardiography. Left ventricular diameters were obtained from parasternal views with optimal orientation to maximize the left ventricular internal diameters as described previously (14). Left ventricular mass was calculated according to the equation proposed by Devereux *et al.* (15): Left ventricular mass = $0.8 \times [1.04 \times \{(\text{interventricular septal thickness} + \text{posterior wall thickness} + \text{end-diastolic diameter})^3 - (\text{end-diastolic diameter})^3\}] + 0.6$. Left ventricular

hypertrophy was defined as left ventricular mass index (left ventricular mass/body surface area) ≥ 125 g/m² for men and ≥ 110 g/m² for women.

Statistical Analysis

Continuous variables are expressed as the mean $\pm$ SD unless stated otherwise and qualitative variables are given as absolute and relative frequencies. Differences between groups were assessed using unpaired *t* test, χ^2 test and one-way ANOVA, as appropriate. For ANOVA, post hoc comparison was performed using the least square difference method. Patients were divided into three groups according to their CRP levels, based on recent recommendations (CRP <1.0 mg/l, CRP 1.0–3.0 mg/l and CRP >3.0 mg/l) (16). Pearson's correlation coefficients were calculated to examine the correlation of CRP with different parameters. To determine independent predictors for elevated CRP concentrations, several baseline characteristics were analyzed by multivariate linear regression using an enter strategy. All the variables shown in Table 1 and which were available for all groups were entered simultaneously into the model, and the least significant was subsequently removed. Then this step was repeated until only significant variables remained in the model. A *p* value of <0.05 (two-tailed) was considered to indicate statistical significance. All statistical analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, USA).

Results

Among 1,500 consecutive adult outpatients, 147 (10%) had never-treated office hypertension. A total of 125 patients were eligible for inclusion in the study. Sixteen patients declined to participate or had incomplete data. Thus, 109 patients with office hypertension were available for analysis.

Baseline characteristics are shown in Table 1. None of the patients or controls received antiplatelet or lipid-lowering therapy. Ambulatory blood pressure values revealed sustained hypertension in 83 patients and white coat hypertension in 26 (24%). Control patients had lower body mass index and higher high-density lipoprotein (HDL)-cholesterol than patients with white coat hypertension, and they had lower triglycerides than patients with sustained hypertension.

There were no statistically significant differences in baseline variables between patients with white coat and sustained hypertension, except for office blood pressure, which was significantly higher in sustained hypertensives (Table 1). Mean ambulatory blood pressure was significantly higher in patients with sustained hypertension than in those with white coat hypertension. The 48 consecutive control patients had age and sex distributions similar to those of the patients with hypertension.

Mean CRP concentrations were 3.4 ± 4.4 mg/l in patients with hypertension. Patients with white coat hypertension had mean CRP levels of 3.2 ± 5.1 mg/l, which was very similar to

the value in patients with sustained hypertension (mean CRP level, 3.4 ± 4.2 mg/l; $p=0.79$). Control patients had lower mean CRP concentrations (1.3 ± 1.0 mg/l) than either patients with sustained or those with white coat hypertension ($p=0.002$ and $p=0.038$, respectively).

Subsequently, patients were divided into three groups according to their CRP concentrations (Fig. 1). The distribution of CRP values did not differ between patients with sustained hypertension and those with white coat hypertension ($p=0.56$). However, the distribution was significantly different between controls and patients with sustained or white coat hypertension ($p=0.021$ and $p=0.009$, respectively). More patients with hypertension were classified in the highest CRP group compared to controls (32.5% and 23.1% vs. 8.3%).

Multiple linear regression analysis revealed BMI as the only independent predictor of increased CRP concentrations ($\beta=0.286 \pm 0.062$; $p<0.001$).

No significant differences in BNP concentrations were found between white coat hypertensives (mean 21 ± 25 pg/ml) and patients with sustained hypertension (mean 44 ± 125 pg/ml; $p=0.35$).

There was no significant correlation between CRP and left ventricular mass ($r=-0.13$, $p=0.21$), and no significant correlation between CRP and E/A ratio ($r=0.05$, $p=0.64$) among all patients with hypertension. These correlations were nearly identical when the analysis was restricted to the 24 patients (92%) with white coat hypertension and available echocardiography (data not shown).

Discussion

The principal finding of this study is that CRP levels are increased in patients with office hypertension according to current guidelines, but do not differ between patients with white coat and those with sustained hypertension. Our data indicate that 30% of patients with hypertension, but only 8% of control patients are at increased cardiovascular risk when stratified according to CRP concentrations (16). To date only one study has investigated CRP levels in never-treated, newly diagnosed patients with sustained and white coat hypertension (3). Our results are in contradiction with the findings of Schillaci *et al.* (3), who found no difference in CRP concentrations between patients with white coat hypertension and healthy controls. The reasons for this difference are unclear. The definition of white coat hypertension is important in the interpretation of study findings (9). However, Schillaci *et al.* (3) used the same definition as in our study (daytime blood pressure below 135/85 mmHg). Hypertensive patients in our study had a higher mean body mass index than those in the study of Schillaci *et al.* It was previously shown that body mass index and CRP concentrations in women are significantly correlated throughout the anthropometric spectrum (17), and our study further confirms this association. Our study was not designed to analyze whether increased CRP levels in patients with white coat hypertension are due to

white coat hypertension itself or just reflect differences in baseline variables. However, the results of our multivariate analysis suggest that white coat hypertension may not be causally involved in increased CRP levels. Another hypothesis may be that patients with white coat hypertension in the present study had a higher prevalence of subclinical arteriosclerosis (18).

Patients with white coat hypertension have BNP concentrations similar to those of patients with sustained hypertension. Unfortunately, data on BNP concentrations were not available in the control group. However, the BNP concentrations in hypertensive patients in our study were clearly higher than those previously reported from a general population (12). Furthermore, Wang *et al.* (19) described significantly lower BNP concentrations in obese compared to nonobese patients. These data suggest that patients with white coat hypertension do have higher BNP concentrations than normotensive controls, indicating an increased risk for cardiovascular events in these patients. Because the use of BNP for risk stratification in individual patients is complicated by a high intraindividual variability (20, 21), further studies are needed to assess the value of single BNP values for cardiovascular risk stratification.

The long-term outcome of patients with white coat hypertension is not well defined. An increased risk for developing sustained hypertension (22) and stroke (23) on long-term follow-up has been reported. Therefore, regular follow-up visits and blood pressure measurements are needed in these patients. The question of whether elevated CRP or BNP concentrations could help to identify patients with white coat hypertension who are at increased cardiovascular risk deserves further study.

The present study has several limitations. The control group was retrospectively matched to the hypertensive patients, and therefore no ambulatory blood pressure measurement was performed. We cannot exclude the possibility that some control-group patients had elevated ambulatory blood pressure despite showing a normal office blood pressure (masked hypertension). However, the presence of individuals with masked hypertension in the control group would have reduced rather than increased the difference in CRP levels. Furthermore, no BNP samples were available in the control group, and the waist-to-hip ratio as a measure of central obesity was not assessed. Finally, patients were recruited from a European, white population, and our results may not be generalizable to nonwhites.

In conclusion, we found that patients with white coat hypertension have concentrations of BNP and CRP similar to those of patients with sustained hypertension. These findings could be of clinical importance, as they may suggest an increased level of inflammation and humoral activation in patients with white coat hypertension. Further studies are needed to establish a potential causal relationship between white coat hypertension and increased inflammatory activity, and to analyze whether this proinflammatory state is associ-

ated with an increased prevalence of subclinical arteriosclerosis and cardiovascular disease.

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