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Original Paper

Combination of Echocardiography and Pulse Wave Velocity Provides Clues for the Differentiation between White Coat Hypertension and Hypertension in Postmenopausal Women

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Key Words

Postmenopause · White coat hypertension · Pulse wave velocity · Left ventricular mass index

Abstract

Objective: To determine whether or not noninvasive assessment of the cardiovascular system can discriminate white coat hypertension and hypertension in postmenopausal women. The major reason is the high prevalence of white coat hypertension in these subjects and the uncertain associations of white coat hypertension with cardiovascular risk. **Patients and Methods:** Selected women were required to be naturally or surgically menopausal for at least 1 year but not more than 5 years past their menstrual period. White coat hypertension patients were defined as subjects who had office blood pressures >150/90 mm Hg but who had both systolic and diastolic ambulatory pressures <120/80 mm Hg. In total, 44 subjects with a mean age of 52 years were recruited from the outpatient clinic and examined. Office and home blood pressures were measured using the HEM 401C (Omron Life Science Co. Ltd., Tokyo, Japan), a semi-automatic device that operates on the cuff-oscillometric principle and generates a digital display of the systolic (SBP) and diastolic blood pressure as well as the pulse rate. The pulse wave velocity (PWV) was recorded, and the left ventricular (LV) diameter, septal wall thickness, and left posterior wall thickness were assessed by M-mode echocardiography after selecting the measurement section by B-mode echocardiography. **Results:** Twenty patients were diagnosed as having white coat hypertension based on the criteria in the trial. Pulse wave patterns were different between subjects with white coat hypertension and those with hypertension. PWV of subjects with white coat hypertension was 1.32 ± 0.33 m/s and that of pa-

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tients with hypertension was 1.46 ± 0.37 m/s ($p < 0.01$). In addition to these findings, there was a significant association between the values of home SBP and PWV and the LV mass index. However, this association was not seen for office SBP. When the data of the LV mass index and PWV were combined, white coat hypertension could be easily differentiated from hypertension. **Conclusions:** The combination of blood pressure self-monitoring, echocardiographic data, and PWV can be a powerful indicator for the treatment of hypertension in postmenopausal women.

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Introduction

Although a general consensus is lacking, it is well known that the blood pressure of women tends to increase during the time around the cessation of menstruation [1–3]. In addition, women have been found to undergo age-related incremental left ventricular (LV) hypertrophy to a greater extent than men [4–6]. Further, it has been shown that women after the menopause have a similar or higher morbidity and mortality from ischemic heart diseases than men. Conversely, it is recognized that lowering systolic blood pressure (SBP) reduces cardiovascular disease mortality [4]. To provide appropriate antihypertensive therapy, it is important to obtain accurate values of blood pressure in individual subjects.

In postmenopausal women, irregularity and cessation of the menstrual cycle induce psychological problems as well as physiological instability, and blood pressure measurements are affected by those factors, resulting in the so-called white coat hypertension [5, 6].

In clinical practice, it remains unknown whether or not white coat hypertension can be considered a benign condition [7–9]. Moreover, the majority of the studies published so far concluded that white coat hypertension was not associated with any significantly increased prevalence of target organ damage [10, 11]. However, Ridd et al. [12] reported that the prevalence of LV hypertrophy was significantly higher in subjects with white coat hypertension than in normotensive individuals.

In women who are diagnosed as having hypertension irrespective of the white coat effect, it is important to detect arterial stiffness, which is considered to be closely associated with LV hypertrophy. In the present study, arterial stiffness was evaluated using pulse wave velocity (PWV) in postmenopausal women who had blood pressure measurements both in the office and at home in conjunction with LV geometry.

Methods

Subjects

In total, 44 women with a mean age of 52 years were recruited from the outpatient clinic and examined. They were required to be naturally or surgically menopausal and past their menstrual period for at least 1 year but not more than 5 years. Exclusion criteria were a history of preeclampsia or eclampsia, a severe illness such as myocardial infarction and stroke within 6 months, the use of estrogens or progestins within 3 months, being treated with antihypertensive agents or nonpharmacological therapy such as the reduction of daily salt, and proteinuric nephropathy. In addition, patients with possible secondary hypertension were excluded.

Definition of White Coat Hypertension

Subjects were defined as having white coat hypertension if they had office blood pressures $>150/90$ mm Hg but had earlier nonoffice readings of both systolic and diastolic ambulatory pressures $<120/80$ mm Hg.

Table 1. Baseline demographic and clinical characteristics of hypertensive and white coat hypertensive postmenopausal women

	Hypertensive (n = 24)	White coat hypertensive (n = 20)
Age, years	53.2 ± 3	53.7 ± 3
Body mass index	24.3 ± 1.2	24.5 ± 1.1
Total cholesterol, mg/dl	201 ± 22	230 ± 8
Fasting glucose, mg/dl	118 ± 5	106 ± 9
Values represent mean ± SD.		

Blood Pressure Measurements in the Clinic [13]

Office blood pressure was measured between 9 and 11 a.m. using a mercury sphygmomanometer; the first and fifth Korotkoff sounds were used to identify systolic and diastolic values, respectively. Two measurements were taken with the patient seated for 5 and 10 min, respectively. The average of these two values was recorded as the office blood pressure at the Kidney Disease Center of the Saitama Medical School Hospital for the inclusion in the study and for determining the efficacy of the treatment.

Home Blood Pressure Measurements

After being shown how to measure their own blood pressure, patients were instructed to record their blood pressure at least twice a week at home in the sitting position – once in the morning before breakfast within 30 min of awakening and once in the evening just before dinner. Home blood pressure was measured using the HEM 401C (Omron Life Science Co. Ltd., Tokyo, Japan), a semi-automatic device that operates on the cuff-oscillometric principle and generates a digital display of the systolic (SBP) and diastolic blood pressure (DBP) as well as the pulse rate. The accuracy of blood pressure self-monitoring was checked by nurses. A standard arm cuff was used to obtain the office and home blood pressure measurements because no patient had an arm circumference of >14 cm.

Pulse Wave Velocity

PWV was measured using an automatic waveform analyzer (form PWV/ABI; Omron Colin, Co., Ltd., Komaki, Japan). Data were collected directly with a portable microcomputer.

Echocardiography

The LV end-diastolic and end-systolic diameters, ventricular septal wall thickness, and left posterior wall thickness were assessed by M-mode echocardiography after selecting the measurement section by B-mode echocardiography. The LV mass index (LVMI) was calculated according to the Penn formula [14]. Data were averaged over 5 cardiac cycles. Throughout the study, echocardiography was performed before treatment and at the end of the study. The interobserver agreement was 90% and the intraobserver agreement was 91%.

Statistical Analysis

Values are given as the mean ± SD. Differences in the echocardiographic and tonometric variables between the white coat hypertension and the essential hypertension group were assessed by nonparametric statistical tests. The Mann-Whitney U test was applied for unpaired values. Simple regression analysis was carried out for PWV and both SBP and DBP. p values <0.05 were regarded as statistically significant.

Results*Patient Characteristics*

Table 1 displays the baseline demographics of the subjects enrolled in this study. There were no significant differences between the two groups.

Table 2. Office and home blood pressure and PWV of hypertensive and white coat hypertensive postmenopausal women

	Hypertensive (n = 24)	White coat hypertensive (n = 20)
Office SBP, mm Hg	167.9 ± 4.8	170.7 ± 6.5
Office DBP, mm Hg	88.5 ± 7.0	91.8 ± 9.1
Home SBP, mm Hg	144 ± 7	123.1 ± 4.3*
Home DBP, mm Hg	84.3 ± 3.8	76.3 ± 7.5*
PWV, m/s	1.46 ± 0.37	1.32 ± 0.33*

Values represent mean ± SEM. * p < 0.05.

Fig. 1. Association between home SBP and PWV in hypertensive (NWC) and white coat hypertensive (WC) postmenopausal women. There is a significant correlation between home SBP and PWV ($p < 0.001$). Home SBP = $116.2 + 16.8 \times \text{PWV}$; $R^2 = 0.271$. **Fig. 2.** Association between office SBP and PWV in hypertensive (NWC) and white coat hypertensive (WC) postmenopausal women. There is a significant correlation between office SBP and PWV in subjects with non-white coat hypertension ($p < 0.05$), but none in those with white coat hypertension. WC: office SBP = $1,106 - 0.66 \times \text{PWV}$; $R^2 = 0.004$. NWC: office SBP = $146 + 16 \times \text{PWV}$; $R^2 = 0.215$. *Differences in Home Blood Pressure, Office Blood Pressure, and PWV between White Coat Hypertension and Essential Hypertension Patients*

SBP and DBP measured in the office were similar between the white coat hypertension and essential hypertension groups. However, home SBP and DBP were significantly lower in the white coat hypertension group than in the essential hypertension group. PWV was also significantly lower in the white coat hypertension group than in the essential hypertension group (table 2).

Table 3. Echocardiographic parameters of hypertensive and white coat hypertensive postmenopausal women

	Hypertensive (n = 24)	White coat hypertensive (n = 20)
PWT, cm	11.5 ± 0.1	10.2 ± 0.2
IVST, cm	11.8 ± 0.3	10.5 ± 0.2
LVDd, cm	42.2 ± 1.0	42.8 ± 0.4
LVDs, cm	32.6 ± 1.0	33.4 ± 0.6
EF, %	79 ± 1	82 ± 1
LVMi	121 ± 7	120 ± 8

Values represent mean ± SEM. PWT = Posterior wall thickness; IVST = intraventricular septal thickness; LVDd = LV diameter of the diastole; LVDs = LV diameter of the systole; EF = ejection fraction.

Fig. 3. Association between office SBP and home SBP in hypertensive (NWC) and white coat hypertensive (WC) postmenopausal women. There is a significant correlation between office SBP and home SBP in subjects with non-white coat hypertension ($p < 0.01$), but none in those with white coat hypertension. NWC: office SBP = $109.57 + 0.401 \times$ home SBP; $R^2 = 0.368$. WC: office SBP = $223.283 - 0.427 \times$ PWC; $R^2 = 0.081$.

There was a significant association between home SBP and PWV ($p < 0.01$) (fig. 1). However, there was no such association for office SBP (fig. 2). Finally, no association was seen between home and office SBP (fig. 3).

Echocardiographic Findings

No echocardiographic variable showed any differences between the white coat hypertension and essential hypertension groups (table 3). However, there was a significant association between LVMi and PWV (fig. 4).

Discussion

White coat hypertension, also referred to as office hypertension or isolated clinic hypertension, is generally defined by a persistently elevated office blood pressure together with a normal blood pressure outside the office. However, there is no consensus about the definition of normal blood pressure outside the office. Some investigators propose the use of daytime ambulatory blood pressure measurements, while others favor 24-hour ambulatory blood pressure measurement [8, 15]. In the present study, blood pressure self-monitoring was employed for the determination of white coat hypertension. The usefulness of self-reported blood pressure monitoring in the diagnosis of white coat hypertension remains to be estab-

Fig. 4. Association between PWV and LVMI in hypertensive (NWC) and white coat hypertensive (WC) postmenopausal women. There is a significant correlation between the LVMI and PWV. $LVMI = 90 + 25 \times PWV$; $R^2 = 0.739$.

lished. In general, blood pressure self-monitoring has not been shown to be accompanied by the white coat effect [16]. Therefore, it has been proposed as a useful alternative to ambulatory blood pressure monitoring in the detection of white coat hypertension [17]. According to several previously reported reference values of self-recorded blood pressures [18, 19], a self-reported SBP >130 – 135 mm Hg and a self-reported DBP >85 mm Hg would be considered hypertensive. Whether or not white coat hypertension is benign remains to be determined [7, 20].

In an analysis of 739 patients followed prospectively for an average duration of 5 years, Pickering [21] demonstrated a prevalence of cardiovascular morbid events of 2.1% in patients with white coat hypertension and of 4.4% in those with sustained hypertension. Some studies found an increased LV mass in subjects with white coat hypertension compared with normotensive controls [22, 23]. The difference in LV mass in the two groups seems to reflect the association between ambulatory blood pressure and LV mass in the normotensive range. LV mass has also been shown to vary significantly with body height, weight, heart rate, and sympathetic activity. While Marcus et al. [24] found that women had an increased LV mass with age in a univariate analysis, only weight remained significant in a multivariate analysis.

These prospective observations of a relatively low cardiovascular risk in white coat hypertension are supported by cross-sectional studies of target organ damage. Sokolow et al. [25] observed that patients with no evidence of target organ damage had a greater difference between office and home blood pressure than patients with target organ damage. In the present study, the LVMI was significantly associated with the SBP measurement at home but not in the office (data not shown), indicating that the levels of self-reported blood pressure monitoring might correlate with the LVMI.

Although casual blood pressure has not shown a strong association with LV mass [24, 26], some recent studies [27, 28] as well as the present study have shown a good correlation between LV mass and PWV. A reason for this apparent anomaly may be the modulating effect of the pulsatile load as compared to the mean vascular load as a significant impetus to myocyte hypertrophy. The gradual increase in LV mass with age in women may therefore be considered an appropriate mechanism to normalize LV wall stress in the face of increased pulsatile load. In addition, we found that the LVMI significantly correlated with PWV in postmenopausal women irrespective of hypertension or white coat hypertension. This finding is in accordance with previous studies reporting that PWV correlated with the degree of LV hypertrophy in humans both at normotensive and hypertensive levels [27, 28]. Moreover, PWV also signifi-

cantly correlated with home SBP in postmenopausal women and showed a greater increase with age independent of any increase in mean arterial pressure [29].

From these data, it appears that in postmenopausal women, ill effects on the heart and arteries are not just merely caused by the elevated resistance and pressure per se, but also by arterial stiffening and higher pulsatile stresses that result from elevated mean pressure. These findings would be an important implication for the treatment of hypertension in postmenopausal women. The blood pressure levels at home, the degrees of PWV, and the LVMi should be measured, and the strategy for antihypertensive treatment should be based on these data. It remains to be seen whether these findings apply to other patient populations than postmenopausal women, although large long-term clinical trials of antihypertensive therapies have included both men and women and have not demonstrated clinically significant sex differences in blood pressure responses and outcomes.

Endothelium-dependent vasodilation is impaired after menopause [30, 31]. Recently, estrogen has been shown to reduce the pulsatile vascular afterload by decreasing the carotid late augmentation of SBP, an index of arterial stiffness [32]. After menopause, the cessation of the beneficial effects of estrogen on arterial vasodilation and structure might determine LV structural changes. Arterial hypertrophy may promote cardiac hypertrophy, at least in part by causing an earlier return of reflected pressure waves from the peripheral circulation [27]. Arterial stiffening, but not hypertrophy, is associated with LV remodeling and is independent of blood pressure. Our finding of an increased relative LV wall thickness, but not mass, after menopause is consistent with these findings.

This study has several limitations. The aim was to determine white coat-related differences in blood pressure in the office and at home using echocardiography and tonometry of the arteries in postmenopausal women. Since the data from normotensive subjects were not obtained, it cannot be determined whether or not our subjects with white coat hypertension are different from normotensive subjects. Second, since these data were obtained using a cross-sectional study, the effects of menopause or hormone withdrawal can be questioned.

In conclusion, the combination of blood pressure self-monitoring, echocardiographic data, and PWV can be a powerful indicator for the treatment of hypertension in postmenopausal women.

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