Original Article

Clinical Significance of Blood Pressure Response Triggered by a Doctor's Visit in Patients with Essential Hypertension

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The clinical significance of the pressor response triggered by blood pressure measurement, the so-called "white-coat effect," was studied in relation to left ventricular structure and function in patients with essential hypertension. We studied 75 consecutive, never-before treated patients with essential hypertension (54 ± 2 (SE) years; 31 men). Beat-to-beat blood pressure (Finapres) was monitored at rest, during conventional blood pressure measurement by a doctor, and during a mental stress test. The left ventricular mass index and diastolic function (*E/A* ratio) were determined by echocardiography. The systolic blood pressure response triggered by the doctor's visit (Δ SBP) correlated positively with the left ventricular mass index ($r = 0.326$, $p < 0.03$) and negatively with the *E/A* ratio ($r = -0.325$, $p < 0.02$). A positive relationship between the Δ SBP and left ventricular mass index was observed in men ($r = 0.556$, $p < 0.01$) but not in women. The greater Δ SBP also was associated with lower *E/A* ratio in women ($r = -0.434$, $p < 0.02$). The Δ SBP correlated with the mental stress-induced increase in systolic blood pressure in men ($r = 0.586$, $p < 0.005$) but not in women ($r = 0.148$, n.s.). Blood pressures outside the clinic were higher in men than in women ($p < 0.05$ for systolic and $p < 0.005$ for diastolic) despite the similar level of clinic blood pressures between the sexes. Stepwise multiple linear regression analysis showed that the Δ SBP was an independent predictor of the left ventricular mass index in men ($\beta = 0.783$, $p = 0.0009$) and of the *E/A* ratio in women ($\beta = -0.003$, $p = 0.05$). These data suggest that the pressor response triggered by a doctor's visit has clinical significance in never-before treated hypertensive patients, possibly because it mirrors real-life stress reactivity in men.

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Key Words: white-coat effect, hypertension, stress, organ damage

Introduction

It has been well established that blood pressure (BP) measurement by a physician triggers a defense reaction which causes a rise in BP (1). Because this pressor response, the so-called "white-coat effect," can lead to a misdiagnosis of hypertension, it is a very important phenomenon to which

physicians must play close attention. In the clinical setting, the pressor response also impinges on treatment in other ways. Blood pressure reactivity to stress has been reported to be associated with a greater cardiovascular risk in men (2) and to be predictive of hypertension (3) and carotid atherosclerosis in post-menopausal women (4). However, it is not clear whether the pressor response triggered by taking a patient's BP has clinical relevance. The clinic-ambulatory dif-

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Fig. 1. Representative beat-to-beat recording of RR interval and systolic and diastolic blood pressures (SBP and DBP, respectively) in a 52-year-old man.

ference in BP has long been used as a surrogate measure of the white-coat effect. Previous studies, however, have shown that the clinic-ambulatory difference in BP correlates positively with clinic BP and negatively with daytime ambulatory BP (5, 6). This means that the clinic-ambulatory difference in BP is not solely a measure of pressor response in the clinic, but rather a variable affected also by environmental factors outside the clinic. Recently, Parati *et al.* (7) developed a unique methodology to evaluate a pressor response in the clinical setting. Beat-to-beat BP was monitored noninvasively at rest and during a visit by the doctor in charge of BP measurement. They defined the difference between the BP response during the doctor's visit and the BP at rest as the "true" white-coat effect. It has been reported that the white-coat response as determined by this new method shows little or no correlation with the clinic-ambulatory difference in BP (7, 8).

Only one report has examined the relationship between the "true" white-coat effect and organ damage; the results showed no relationship between the white-coat effect and left ventricular structure (8). However, these results are less than conclusive because 1) only 50% of the 88 echocardiographic studies performed were of sufficient quality to calculate the left ventricular mass reliably; and 2) 27% of subjects were on antihypertensive medication. The inclusion of treated patients might have modified the relationship between the "true" white-coat effect and organ damage. Furthermore, the issue of gender difference in the effects of pressor response to a doctor's BP measurement on organ damage has not been addressed. We previously showed that type A behavior is an independent predictor of left ventricular hypertrophy in men, but not women, with essential hypertension (9). Because type A behavior is known to modulate cardiovascular and

endocrine reactivity to environmental stress, the influence of the pressor response in the clinic on the heart may differ between men and women. The aim of this study was to determine whether the white-coat effect, as determined by beat-to-beat BP monitoring, is related to left ventricular structure and function in never-before treated patients with essential hypertension, and if so, whether any gender-related difference exists.

Methods

Subjects

We evaluated 75 consecutive outpatients (31 men and 44 women) with essential hypertension (World Health Organization stage I or II) whose BP was ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic during at least three visits at 1-week intervals. All of the patients reported that they were not receiving and had not previously received drug treatment for hypertension. Patients with secondary hypertension or with autonomic disturbance were excluded from the study. Twenty-eight men (90%) were currently employed while 40 women (91%) were housewives or retired. Only 8 women reported regular menstruation. The study protocol was approved by the Ethics Committee of Tohoku Rosai Hospital. Informed consent to participate in our study was obtained from all patients.

Cardiovascular Response to BP Measurement and Mental Stress

Patients were studied in a quiet room after a light breakfast. The ECG was monitored using a standard lead II with the

Table 1. Demographic and Clinical Characteristics of Subjects

Variable	All	Male	Female	<i>p</i>
Age (y)	54 ± 2	47 ± 2	59 ± 2	0.0002
Clinic systolic blood pressure (mmHg)	168 ± 2	164 ± 4	170 ± 3	n.s.
Clinic diastolic blood pressure (mmHg)	99 ± 1	100 ± 1	99 ± 1	n.s.
Body mass index (kg/m ²)	24.8 ± 0.5	26.0 ± 1.0	24.0 ± 0.5	0.04
Fasting blood sugar (mmol/l)	5.6 ± 0.1	5.8 ± 0.2	5.4 ± 0.1	0.002
Total cholesterol (mmol/l)	5.7 ± 0.1	5.9 ± 0.2	5.6 ± 0.1	0.03
Triglycerides (mmol/l)	1.4 ± 0.1	1.8 ± 0.2	1.1 ± 0.1	0.00001
HDL-cholesterol (mmol/l)	1.6 ± 0.1	1.4 ± 0.1	1.7 ± 0.1	0.003
Renin (ng/L/s)	0.23 ± 0.04	0.35 ± 0.08	0.14 ± 0.03	0.009
Aldosterone (pmol/l)	213.3 ± 15.0	243.8 ± 22.2	185.6 ± 19.4	0.05
Left ventricular mass index (g/m ²)	105 ± 3	114 ± 6	99 ± 4	0.02
Fractional shortening (%)	39 ± 0.8	37 ± 1	41 ± 1	0.03
<i>E/A</i> ratio	0.98 ± 0.04	1.06 ± 0.07	0.92 ± 0.04	n.s.

HDL, high-density lipoprotein; n.s., not significant.

patients in the supine position. A digital photoplethysmographic device (Finapres 2300; Ohmeda, Englewood, USA) was attached to the right middle finger to measure BP. The validity, reliability, and clinical application of the Finapres device have been confirmed previously (10). Measurements were obtained after patients had rested for 15 min to allow hemodynamic stabilization. We measured the beat-to-beat BP (Finapres) and RR interval (ECG) during a 10-min resting period, an 8-min visit by a doctor not familiar to the patient who measured the patient's BP by sphygmomanometer, and a 6-min interval of mental stress created by asking the patient to count backwards (Fig. 1). The order of the doctor's visit and the mental stress were alternated randomly with a 15-min recovery period between them. Blood pressures were measured three times at 2-min intervals during the doctor's visit. The mean systolic and diastolic BPs and the RR interval were calculated for each condition. The BP response to the doctor's visit, *i.e.*, the "true" white-coat effect, and the BP response to mental stress were defined as the difference between the BP obtained during the doctor's visit or mental stress test and that obtained with the patients at rest. We calculated the maximal white-coat effect and BP response to stress by subtracting the peak BP during the doctor's visit or mental stress test and the BP at rest.

Echocardiography

M-mode, two-dimensional echocardiography was performed by two well-trained physicians (M.M. and T.N.) using a commercially available instrument (Hewlett Packard SONOS 2500; Hewlett Packard, Andover, USA) equipped with a 2.5/2.0 MHz imaging transducer. Left ventricular internal diameters and parietal thickness were calculated from two-dimensional guided M-mode tracing and measured in 3 to 5 consecutive cardiac cycles according to the recommendations of the American Society of Echocardiography. Only

frames that afforded an optimal visualization of the interfaces and that simultaneously showed the interventricular septum, left ventricular internal diameter and posterior wall were employed. Left ventricular mass was calculated according to the Penn convention and normalized with respect to body surface area. The early diastolic peak flow velocity (*E*), late diastolic peak flow velocity (*A*), and the ratio of *E* to *A* (*E/A*) were recorded using a sample volume at the mitral leaflet tips. Intra- and interobserver coefficients of variation for the left ventricular mass index (LVMI) were 7.9% and 8.4%, respectively (9).

Blood Pressure Measurement in and outside the Clinic

Blood pressures were measured in the clinic by a physician using a semi-automated, oscillometric device (TM2710; A&D, Tokyo, Japan) after 5 min of rest. Three measurements were obtained within a 7- to 10-min period with the patient seated. The average of the last 2 measurements was used as the clinic BP. The clinic BPs obtained during the third clinic visit were used for data analysis. Blood pressures were also monitored over 24 h using the TM2421 device (A&D), which was programmed to obtain BP readings at 30-min intervals. Ambulatory BP monitoring was performed on a work day. During monitoring, patients were asked to attend to their routine activities, but to avoid unusual physical exercise and to keep the arm involved in the automatic BP measurement extended and immobile at the time of each cuff inflation. Ambulatory BP data were analyzed to obtain the mean daytime (6:00 to 21:00) and 24-h values.

Statistical Analysis

Data are reported as the mean ± SEM. Paired or unpaired Student's *t*-tests were used to compare differences between

Table 2. Blood Pressures at Rest, during the Doctor's Visit and during Mental Stress

Variable	All	Male	Female	<i>p</i>
Resting				
Systolic blood pressure (mmHg)	132 ± 2	136 ± 4	130 ± 3	n.s.
Diastolic blood pressure (mmHg)	73 ± 2	75 ± 2	71 ± 2	n.s.
During doctor's visit				
Mean systolic blood pressure (mmHg)	147 ± 3 [‡]	150 ± 5 [‡]	146 ± 4 [‡]	n.s.
Mean diastolic blood pressure (mmHg)	81 ± 2 [‡]	83 ± 3 [‡]	80 ± 3 [‡]	n.s.
Peak systolic blood pressure (mmHg)	168 ± 3 [‡]	170 ± 6 [‡]	166 ± 4 [‡]	n.s.
Peak diastolic blood pressure (mmHg)	94 ± 3 [‡]	92 ± 3 [‡]	91 ± 3 [‡]	n.s.
During mental stress				
Mean systolic blood pressure (mmHg)	153 ± 4 [‡]	165 ± 7 ^{‡,†}	145 ± 4 [‡]	0.01
Mean diastolic blood pressure (mmHg)	83 ± 2 [‡]	85 ± 2 ^{‡,†}	81 ± 2 [‡]	n.s.
Peak systolic blood pressure (mmHg)	174 ± 4 [‡]	183 ± 9 ^{‡,*}	168 ± 5 [‡]	0.07
Peak diastolic blood pressure (mmHg)	93 ± 3 [‡]	100 ± 3 ^{‡,†}	90 ± 3 [‡]	0.05

* $p < 0.05$, [†] $p < 0.005$ vs. during the doctor's visit; [‡] $p < 0.001$ vs. resting. n.s.: not significant.

Table 3. Mean and Maximum Blood Pressure Change during the Doctor's Visit and Mental Stress

Variable	All	Male	Female	<i>p</i>
Mean change during doctor's visit				
Systolic blood pressure (mmHg)	15 ± 3	15 ± 4	15 ± 3	n.s.
Diastolic blood pressure (mmHg)	8 ± 1	7 ± 2	9 ± 2	n.s.
Maximum change during doctor's visit				
Systolic blood pressure (mmHg)	36 ± 3	33 ± 4	38 ± 4	n.s.
Diastolic blood pressure (mmHg)	19 ± 1	17 ± 2	20 ± 2	n.s.
Mean change during mental stress				
Systolic blood pressure (mmHg)	21 ± 3	28 ± 5	15 ± 4	0.03
Diastolic blood pressure (mmHg)	10 ± 1	13 ± 2	8 ± 2	0.04
Maximum change during mental stress				
Systolic blood pressure (mmHg)	43 ± 3	47 ± 6	39 ± 4	n.s.
Diastolic blood pressure (mmHg)	21 ± 1	24 ± 2	19 ± 2	n.s.

n.s.: not significant.

means. Correlation coefficients were calculated by Pearson's product-moment. The relationship between echocardiographic parameters and other parameters were evaluated using stepwise multiple regression analysis. All statistical analyses were performed using commercially available software (Stat Flex ver. 5.0 for Windows; Artec, Osaka, Japan).

Results

The demographic and clinical characteristics of the study group are summarized in Table 1. Clinic BPs were similar between men and women. However, gender-related differences were observed for several variables. The men were younger than the women ($p = 0.0002$), and had a higher body mass index (BMI) ($p = 0.04$), fasting serum glucose concentration ($p = 0.002$), total serum cholesterol concentration ($p = 0.03$), and serum triglycerides concentration ($p = 0.00001$), and a lower serum concentration of high-density

lipoprotein (HDL)-cholesterol ($p = 0.003$). Plasma renin activity and plasma aldosterone concentrations also were higher in men than in women ($p = 0.009$ and $p = 0.05$, respectively). We obtained reliable echocardiographic measurements in 63 of 75 subjects (84%). The LVMI was greater and the fractional shortening was lower in men than in women ($p = 0.02$ and $p = 0.03$, respectively). The E/A ratio was similar in the two groups.

Table 2 shows the BPs at rest, during the doctor's visit, and during the mental stress test as measured by the Finapres device. Blood pressures were similar in men and women both at rest and during the doctor's visit, while the mean systolic BP and the peak systolic and diastolic BPs during stress were higher in men ($p = 0.01$, $p = 0.07$ and $p = 0.05$, respectively). Neither the mean nor the peak BP responses to the doctor's visit were different between men and women, while mean BP responses to mental stress were greater in men ($p = 0.03$ for systolic and $p = 0.04$ for diastolic) (Table 3).

Fig. 2. Relationship between systolic blood pressure response to the doctor's visit and systolic blood pressure response to mental stress in men (left panel) and women (right panel) with essential hypertension.

Fig. 3. Relationship between systolic blood pressure response to the doctor's visit and left ventricular mass index in men (left panel) and women (right panel) with essential hypertension.

The systolic BP response to the doctor's visit correlated with the mental stress-induced increase in systolic BP in men ($r = 0.586$, $p < 0.01$) but not in women ($r = 0.148$, n.s.) (Fig. 2). Day time ambulatory BPs were higher in men than in women ($150 \pm 2/93 \pm 2$ vs. $143 \pm 2/84 \pm 2$ mmHg; $p < 0.05$ for systolic and $p < 0.005$ for diastolic, respectively), although clinic BPs were similar. Consequently, the clinic-ambulatory difference in BP was smaller in men than in women ($14 \pm 3/8 \pm 2$ vs. $28 \pm 3/14 \pm 2$ mmHg; $p < 0.03$ for both). The clinic-ambulatory difference in systolic BP demonstrated a marginal and significant positive correlation with systolic BP response triggered by the doctor's visit in men and women ($r = 0.364$, $p = 0.07$ and $r = 0.442$, $p = 0.007$, respectively).

In the simple correlation analysis of all subjects, the systolic BP response to the doctor's visit was correlated posi-

tively with the LVMI ($r = 0.326$, $p < 0.03$) and negatively with the E/A ratio ($r = -0.325$, $p < 0.02$). The larger systolic BP response to the doctor's visit was associated with a greater LVMI in men ($r = 0.556$, $p < 0.01$) but not in women ($r = 0.09$, n.s.) (Fig. 3). The systolic BP response to the doctor's visit correlated negatively with the E/A ratio in women ($r = -0.434$, $p < 0.02$). In men, the LVMI correlated also with 24-h mean systolic BP ($r = 0.493$, $p < 0.05$). In multiple linear regression analysis that included the systolic BP response to the doctor's visit and 24-h mean systolic BP as independent variables, the LVMI was correlated with both parameters ($\beta = 0.783$, $p = 0.0009$ and $\beta = 1.3385$, $p = 0.003$, respectively). The E/A ratio correlated with age ($r = -0.510$, $p < 0.01$), stress-induced increase in the systolic BP ($r = -0.626$, $p < 0.005$), and clinic-ambulatory difference in sys-

tolic BP ($r = -0.512$, $p < 0.02$). Multiple regression analysis, however, revealed that the *E/A* was correlated only with age ($\beta = -0.0013$, $p = 0.01$) and stress-induced increase in systolic BP ($\beta = -0.007$, $p = 0.02$). In women, the LVMI correlated with 24-h mean systolic BP ($r = 0.437$, $p < 0.01$) and plasma renin activity ($r = -0.403$, $p < 0.05$). The *E/A* correlated with age ($r = -0.444$, $p < 0.01$) and 24-h mean systolic BP ($r = -0.458$, $p < 0.01$), as well as with the systolic BP response to the doctor's visit. In multiple regression analysis, the LVMI was correlated only with 24-h systolic BP ($\beta = 0.717$, $p = 0.008$) and the *E/A* correlated with age ($\beta = -0.006$, $p = 0.06$), 24-h systolic BP ($\beta = -0.005$, $p = 0.05$) and systolic BP response to the doctor's visit ($\beta = -0.003$, $p = 0.05$).

Discussion

This study examined the relationship between the pressor response triggered by a doctor's visit, *i.e.*, the "true" white-coat effect, and left ventricular structure and function in never-before treated hypertensive patients. We found that the pressor response triggered by the doctor's visit was an independent predictor for LVMI in men. This parameter also was an independent predictor of the *E/A* ratio in women. These data suggest that the white-coat effect has clinical significance.

The independent association of the BP response triggered by the doctor's visit and the LVMI in men strongly suggests that the pressor response in medical situations reflects an underlying degree of pressor reactivity, since it hardly seems likely that one or two clinical pressor responses per month would be able to induce myocardial hypertrophy. In fact, men showed a positive correlation between the BP response to the doctor's visit and a stress-induced increase in BP, while women did not. These data suggest that the "true" white-coat effect predicts BP reactivity to mental stressors in men. We believe that the pressor response in the clinic correlates with BP reactivity to real life stresses in men, which is why it predicts LVMI.

The independent association between a greater pressor response triggered by the doctor's visit and greater impairment of left ventricular diastolic function in women suggests that the white-coat effect is also harmful to women. However, we cannot rule out the possibility that this relationship represents a temporary increase in myocardial stiffness due to the adrenergic response pertinent to undergoing an echocardiogram. Furthermore, the correlation coefficient between the LVMI and the BP response to the doctor's visit was very low in women ($r = 0.09$). This issue requires a long-term prospective study to determine whether the pressor response in the clinic situation promotes myocardial hypertrophy in women over time.

Why is it that only men showed generalized BP responses to the doctor's visit and to mental stress? Since a prompt BP response to the doctor's visit or to mental stress is mediated mainly by the sympathetic nervous system (11), our data

suggest a sex-related difference in sympathetic cardiovascular regulations. In fact, there is growing evidence that sex affects the regulation of the sympathetic nervous system. It has been shown that pathways regulating the sympathetic nervous system appear to be more sensitive to excitatory stimuli and less sensitive to inhibitory stimuli in men than in women (12). This means that a similar level of external stimuli would more easily and/or more markedly induce excitation of the sympathetic nervous system in men than in women, and would seem to offer a good explanation of the present results. The greater BP reactivity to mental stress in men may be attributable to personality characteristics as well. We previously showed that type A personality, a coronary-prone character, is more common among hypertensive men than hypertensive women (9). Type A behavior is well known to be characterized by greater reactivity of cardiovascular systems in response to psychosocial stress (13).

Our data showed that greater BP reactivity in the clinic should be considered as a significant risk factor for cardiovascular disease in hypertensive men. These findings are in line with the previous report that subjects with hyperreaction to stressful situations may develop initial changes of the left ventricle, even if their 24-h BP load is normal (14), and highlights the clinical importance of office BP readings in hypertension treatment. Our data may also support the notion of the clinical importance of blood pressure variability in hypertension treatment (15–17). To further clarify our hypothesis, an interventional study will be needed to examine whether restraint of the pressor response in the clinic could reduce left ventricular hypertrophy in hypertensive men.

Our data are inconsistent with those of a previous report in which the BP response triggered by a doctor's measurement of BP did not correlate with any other pressor response induced by laboratory stressors (18). However, that report differed from ours in several important ways. First, the study cohort included only 22 subjects, 13 normotensive and 9 mildly hypertensive subjects. Thus the sample size was small and its members were very different than ours. Because the white-coat effect is virtually absent in normotensives, the positive correlation between the white-coat effect and a stress-induced increase in BP may be less detectable in such a group. Second, the experimental setting was different. These investigators studied inpatients 1 week after hospital administration, while our all subjects were outpatients. The 1-week hospitalization may have reduced the baseline stress level, and might have altered the neuroendocrine milieu as well.

In a previous study, Lantelme *et al.* (8) found no correlation between the BP response triggered by a doctor's visit and left ventricular structure in hypertensive subjects. This discrepancy with our present results may have arisen due to several factors. First, in Lantelme's study, the LVMI was calculated in only 50% of the 88 subjects, vs. 84% of the 75 subjects in our study. Thus, we had greater statistical power to detect the relationship between pressor response to the

doctor's visit and the LVMI. Second, the subjects in our study were older (54 vs. 50 years) and the LVMI was greater (105 vs. 94 g/m²). Thus our subjects would have spent a longer time under the influence of factors which produce pressor reactivity than the patients in the previous report. In addition, we studied only antihypertensive-naïve patients, while 27% of the subjects in the previous report had received antihypertensive medication. The inclusion of treated patients might have modified the relationship between the "true" white-coat effect and organ damage.

Finally, two additional points deserve to be mentioned. First, correlations between the clinic-ambulatory difference in BP and pressor response to the doctor's visit were weak in both men and women. This means that the clinic-ambulatory difference in BP is a rough measure of the true white-coat effect. In fact, the clinic-ambulatory difference in BP was 2 times greater in women than in men, although pressor response to the doctor's visit did not differ between them. Because clinic BPs did not differ between the two groups, the greater clinic-ambulatory difference in BP in women was due chiefly to lower ambulatory BP. The clinic-ambulatory difference in BP has been widely used as a surrogate measure of the white-coat effect, but we should bear in mind that this measure could be influenced largely by depressor factors outside the clinic. Second, the men in our study presented very different demographic and clinical characteristics than the women. These differences are unlikely to be due to selection bias, since we studied consecutive, never-before treated hypertensive patients. In other words, our subjects can be considered representative of newly diagnosed hypertensive patients in urban areas of Japan.

In conclusion, the pressor response triggered by BP measurement is of clinical relevance in never-before treated hypertensive patients. The effect was greater in men than women, possibly because the "true" white-coat effect more closely mirrors the stress-related BP reactivity that men experience in daily life. To further confirm our hypothesis, we will need to examine whether a restraint of BP response during a doctor's visit could reduce left ventricular hypertrophy in hypertensive men.

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