White-coat hypertension (WCH) is defined as an elevated blood pressure (BP) that manifests only in the doctor’s office, whereas the patient’s average daytime BP measured elsewhere is within the normal range. The prevalence of WCH is estimated to be 20–40% of hypertensive patients. It is unclear whether the cardiovascular risk of patients with WCH differs from that of people with essential hypertension (EH) or normotension (NT).

Several studies have reported that individuals with WCH have cardiovascular risk and target organ damage similar to those of normal individuals. However, other studies have reported that people with WCH have a significantly higher cardiovascular event rate and target organ damage. Greater LVH, carotid intima–media thickness, and microalbuminuria, and impaired LV diastolic function were higher in hypertensive patients with LVH than in normotensive controls.

It is thought that LVH detected in hypertensive patients is caused by myocyte hypertrophy and myocardial fibrosis, and that the myocardial fibrosis in particular causes the changes in cardiac function including LV diastolic dysfunction. LVH and LV diastolic dysfunction have been widely recognized as predictors of cardiovascular morbidity and mortality in hypertensive patients. Subtle modifications in LV structure and geometry may occur in the early phase of EH, and myocardial fibrosis plays a major role. Accordingly, many investigators are interested in the quantification of myocardial fibrosis. Endocardial biopsy is certainly the gold standard in this regard but for ethical reasons it is limited.

Moreover, transforming growth factor (TGF)-β1 is known to play an important role in myocardial fibrosis by stimulating the synthesis of matrix molecules in hypertensive heart disease. Several recent studies have detected myocardial fibrosis early in the course of hypertension and shown that it precedes the development of LV diastolic dysfunction and LVH.

Because long-term follow-up results of WCH patients have shown they have higher cardiovascular event rates, the detection of target-organ changes is very useful in their clinical management. To the best of our knowledge, no study concerning myocardial fibrosis in WCH has been performed.

In the present study, we compared target organ status,
such as LVH, parameters of LV diastolic function, and biochemical markers of myocardial fibrosis (concentrations of TGF-β1 and PIP) in individuals with NT, WCH, and EH. We also ascertained the correlation between the biochemical markers of myocardial fibrosis and indices of LV diastolic function in patients with WCH.

**Methods**

**Study Population**

The patients had mild to moderate hypertension, defined as office systolic BP of 140–159 mmHg or office diastolic BP of 90–99 mmHg. They were aged between 30 and 70 years of age, and were not taking antihypertensive drugs. None of the participants had clinical or laboratory evidence of coexisting cardiovascular disease (on chest radiography or electrocardiography) and had no echocardiographic evidence of valvular heart disease, cardiomyopathy (LV ejection fraction (LVEF) <55%), or history of diabetes or nephropathy (Cr >1.2 mg/dl). The study population excluded patients with disorders evident within the previous year that could affect PIP or TGF-β1 concentrations, such as acute inflammation, arthritis, proteinuria, hematuria, diabetes or treatment with lipid-lowering agents.

Office BP readings were taken 3 times by a trained physician after the patient had rested for 15 min in the sitting position during the morning (08.00–10.00 h) using an appropriate-sized arm cuff and a mercury sphygmomanometer. Three readings were taken at intervals of 5 min, and the mean was calculated. Official hypertension defined as an office systolic BP >140 mmHg and/or an office diastolic BP >90 mmHg.

All participants underwent 24 h monitoring of ambulatory BP (ABP) on a normal working day. Office BP and 24-h ABP were recorded on the same day. A pressorometer IV ABP monitor (Model 1990A/1991, Del Mar Avionics, Irvine, CA, USA) was attached to the nondominant arm. Systolic and diastolic ABP were recorded on the same day. A pressurometer after the patient had rested for 15 min in the sitting position during the morning (08.00–10.00 h) using an appropriate-sized arm cuff and a mercury sphygmomanometer. Three readings were taken at intervals of 5 min, and the mean was calculated. Official hypertension defined as an office systolic BP >140 mmHg and/or an office diastolic BP >90 mmHg.

Echocardiography

Echocardiograms were recorded using a commercially available ultrasound system (Sonos 5500, Hewlett Packard, Andover, MA, USA). Subjects were examined in the left lateral decubitus position using standard parasternal and apical views with a 2.5-MHz transducer. Pulsed Doppler echocardiographic measurements of transmitral flow velocity profiles were performed by positioning a sample volume within 2 mm of the tip of the mitral valves in the apical 4-chamber view. The other index of LV diastolic relaxation was determined from the ratio of peak transmitral E velocity to early diastolic mitral annular velocity (E/E')

Laboratory Parameters and Quantification of Myocardial Fibrosis

General biochemical parameters, including the concentrations of blood glucose, serum creatinine, total cholesterol and triglycerides, and 24-h urine microalbuminuria were measured using routine laboratory analytical methods. A peripheral venous blood sample was obtained from each subject, and the serum was isolated and stored at –70°C until assayed for TGF-β1 and PIP. The serum was acidified, and the concentration of biologically active TGF-β1 protein was determined using a solid-phase TGF-β1-
specific sandwich ELISA (Quantikine Human TGF-β1 ELISA, R&D System, Oxford, UK). The intra- and interassay variation for determining TGF-β1 was 7% and 10%, respectively. The minimum detectable concentration of TGF-β1 is 5 pg/ml. Serum PIP concentration was determined using a precoated type 1 step sandwich enzyme immunoassay with monoclonal anti-human procollagen type I (Takara Bio, Shiga, Japan). The intra- and interassay variation for determining PIP was 6% and 8%, respectively. The minimum detectable concentration of PIP is 10 ng/ml.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 10.0 (SPSS, Inc, Chicago, IL, USA). Continuous variables with a normal distribution are expressed as mean±SD and compared using ANOVA with Scheffe’s post hoc test if the results of the ANOVA were significant. Categorical variables were compared with the χ² test, as appropriate. Linear regression analysis was used to assess the correlation between E/E' and PIP in the WCH group. All comparisons were 2-sided, and P-values <0.05 were regarded as significant.

Results

Clinical Characteristics

The mean age of the WCH, EH and NT patients was 48±8 years, 48±9 years, 51±7 years, respectively, and 60%, 68% and 43% of each group were women. Mean age and sex distribution did not differ significantly between groups.

Body mass index, the concentrations of serum glucose, creatinine, total cholesterol and triglyceride, and 24-h microalbuminuria results did not differ significantly between groups (Table 1).

By definition, office BP was significantly higher in the patients with WCH and EH than in the NT group. Mean daytime and night-time ABP were higher in the EH group than in the other 2 groups. Mean daytime and mean night-time ABP did not differ significantly between the WCH and NT groups (Fig 1).

Echocardiographic Data (Table 2)

The IVS, PWT and LVEDD were larger in the EH group than in the WCH group, but there was no significant difference among the 3 groups in LVMI (index of LV systolic function). The LVEF (indicator of LV systolic function) was significantly lower in the EH group than in the other 2 groups.

<table>
<thead>
<tr>
<th></th>
<th>NT (n=30)</th>
<th>WCH (n=30)</th>
<th>EH (n=30)</th>
<th>ANOVA P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVST (mm)</td>
<td>10.0±1.4</td>
<td>10.6±1.6</td>
<td>13.5±2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>45.5±2.9</td>
<td>44.6±3.9</td>
<td>46.9±3.0</td>
<td>0.028</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>28.0±2.8</td>
<td>27.2±3.2</td>
<td>28.9±2.8</td>
<td>0.088</td>
</tr>
<tr>
<td>PWT (mm)</td>
<td>10.1±1.1</td>
<td>10.5±1.3</td>
<td>13.1±2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>65.8±3.7</td>
<td>65.8±3.6</td>
<td>64.6±3.3</td>
<td>0.343</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>70±11</td>
<td>79±16</td>
<td>102±24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MV E/A ratio</td>
<td>1.28±0.30</td>
<td>1.10±0.31</td>
<td>0.94±0.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MV DT (ms)</td>
<td>178±36</td>
<td>181±49</td>
<td>201±60</td>
<td>0.121</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>90±10</td>
<td>85±13</td>
<td>99±18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV E/E'</td>
<td>7.58±1.92</td>
<td>9.01±1.74</td>
<td>10.01±2.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PIP (ng/ml)</td>
<td>95.7±18.4</td>
<td>118.3±23.1</td>
<td>119.1±25.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TGF-β1 (ng/ml)</td>
<td>63.9±30.9</td>
<td>91.1±24.5</td>
<td>86.7±37.7</td>
<td>0.002</td>
</tr>
</tbody>
</table>

1P<0.05 NT vs WCH, 2P<0.05 WCH vs EH.

IVST, interventricular septal thickness; LV, left ventricle; EDD, end-diastolic dimension; ESD, end-systolic dimension; PWT, posterior wall thickness; EF, ejection fraction; MI, mass index; MV, mitral valve; DT, deceleration time; IVRT, isovolumic relaxation time; PIP, procollagen type I propeptide; TGF, transforming growth factor. Other abbreviations see in Table 1.
was larger than in the NT group and smaller than in the EH group. Among the indices reflecting LV diastolic function, the LV E/A ratio of the mitral inflow pattern using Doppler in the WCH group was significantly lower (1.10±0.31) than in the NT group (1.28±0.30) and significantly higher than in the EH group (0.89±0.33) (ANOVA, P<0.001). DT did not differ significantly among the 3 groups. IVRT was shorter in the WCH group (85±13 ms) than in the NT (90±10 ms) or EH group (99±18 ms) (ANOVA, P<0.001). The LV E/E' ratio, another index of LV diastolic function, in the WCH group (9.01±1.74) was higher than in the NT group (7.58±1.92) and lower than in the EH group (10.01±2.09) (P<0.001).

Biochemical and Other Markers (Table 2)

The concentration of serum PIP, which is associated with collagen synthesis, was significantly higher in the WCH group (118.3±23.1 ng/ml) than in the NT group (95.7±18.3 ng/ml) (P<0.001), but did not differ from the concentration in the EH group (119.1±25.9 ng/ml). Similarly, the serum TGF-β1 concentration in the WCH group was higher than in the NT group (P<0.001) and slightly, but not significantly, lower than in the EH group.

The relationships between PIP or TGF-β1 (biochemical markers of collagen synthesis) and other echocardiographic Doppler indices were examined. The correlation between serum PIP concentration and the LV E/E’ ratio (which reflects an estimate of the LV diastolic dysfunction) was significant in all participants, as well as in the WCH group (r=0.33, P=0.001) (Fig 2). Linear regression analysis of serum PIP concentration and the LV E/E’ ratio in the WCH group produced a significant correlation (r=0.39, P=0.03) (Fig 3).

Discussion

Studies investigating whether WCH patients have cardiovascular target organ damage have produced contradictory results.14-17 In the present study, we compared target organ status from the aspect of LVH, diastolic dysfunction and myocardial fibrosis in patients with WCH, EH and NT. An association between the biochemical markers of myocardial fibrosis and the indices of LV diastolic indices was noted in patients with WCH.

Status of Target Organ Damage in WCH

The LVMI reflects LVH and was lower in the WCH group than in the EH group, but was higher than in the NT group, which suggests that, with respect to LVH, WCH patients are an intermediate group between NT and EH. Similarily, the indices used to evaluate LV diastolic function were intermediate in the WCH group, an observation consistent with previous reports by Chang et al12 and Celis et al.26

In hypertension, structural changes in the LV caused by myocyte hypertrophy and myocardial fibrosis occur before the development of LVH.14,17 Myocardial fibrosis is an important cause of LV diastolic dysfunction and may be an important early event in target organ damage.14,17 Therefore, we compared the concentrations of TGF-β1 and PIP, biochemical markers of myocardial fibrosis,17-25 between the 3 groups. These biochemical markers have been well correlated with CVF on endocardial biopsies in hypertensive patients,18-20 and in the present study the levels of both markers were higher in the WCH than in the NT group, but did not differ between the WCH and EH group, which was consistent with the finding of increased myocardial fibrosis in the WCH group compared with the NT group. However, the concentrations of the biomarkers of myocardial fibrosis were similar in the EH and WCH groups. It is possible that these markers of myocardial fibrosis might be associated with the duration or severity of hypertension.

Myocardial Fibrosis and LV Diastolic Dysfunction in WCH

The only biochemical marker of myocardial fibrosis that correlated with the Doppler indices representing LV diastolic function was serum PIP concentration. PIP concentration correlated with LV E/E’ ratio (r=0.33, P<0.001) in all groups, and in the WCH group (r=0.39, P=0.03), particularly, the LV E/E’ ratio measured with Doppler, which is now frequently used as an index of LV diastolic dysfunction. This index is an estimate of LV diastolic dysfunction and the stiffness of the LV wall, and is accepted as a sensi-
Possible Pathophysiology of Target Organ Damage in WCH

There are several possible mechanisms of the increase in cardiovascular complications reported in individuals with WCH. The first relates to elevated sympathetic nervous system activity, which can cause abnormalities in the variation of diurnal BP and pulse pressure, which can induce target organ damage. The second involves insulin resistance. Individuals with WCH are more likely to be obese than are people with NT and they may have abnormalities in glucose or lipid metabolism or insulin resistance. A third possibility is that oxidative stress or endothelial dysfunction may accelerate vascular atherosclerosis. It is thought that early atherosclerosis develops by 1 or a combination of these mechanisms and that these changes induce target organ damage and cardiovascular abnormalities.

Study Limitations

The major limitation of our study is that we were unable to directly measure the level of myocardial fibrosis to determine the association between the biochemical markers of myocardial fibrosis. For ethical reasons, we did not perform endocardial biopsy, the most reliable means of measuring myocardial fibrosis, because of the invasive nature of the method. Therefore, we used a relevant biochemical marker of myocardial fibrosis, because of the invasive nature of the method. Thus, the biochemical marker of myocardial fibrosis was used by other groups to study other cardiac diseases.

Among the indices of LV diastolic function, only LV E/E' was significantly correlated with PIP levels. However, other indices (LV E/A ratio, DT and IVRT) were not significant. The study consisted of a small number of patients to conclude the relationship between diastolic dysfunction and PIP levels in WCH. Small sample size might have caused this discrepancy, and therefore a larger sample size would be necessary to reduce such a discrepancy.

The 24-h urine microalbuminuria values tended to be higher in the WCH and EH groups than in the NT group, although these differences were not significant. Previous studies have reported greater microalbuminuria, which reflects early target organ damage in the kidney, in individuals with WCH compared with individuals with NT. In contrast, we found no significant difference, possibly because of the small sample size.

Our study is the first to compare PIP concentration, a biochemical marker of myocardial fibrosis, with the index of LV diastolic dysfunction in WCH patients. We found that target organ damage in WCH patients was intermediate between individuals with NT and EH, and that PIP concentration correlated with LV diastolic dysfunction, suggesting that PIP concentration reflects target organ damage associated with LV. The quantification of myocardial fibrosis might be important for early prediction of those patients who will go on to develop abnormalities in the cardiovascular system. Together with echocardiographic Doppler parameters, the serum PIP concentration may be a useful test for early diagnosis and screening for myocardial fibrosis and thus to predict the prognosis of individuals with WCH. WCH patients who have cardiac functional and structural abnormalities might benefit from early intervention (including antihypertensive therapy) to prevent cardiovascular events. A longitudinal study of a large number of patients is necessary to reveal more clearly the long-term prognostic value in WCH patients.

References


