Sympathetic Neural Mechanisms in White-Coat Hypertension
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OBJECTIVES
This study planned to establish whether sympathetic hyperactivity exists in white-coat hypertension (WHT) in the clinical setting, relative to matched groups with normotension (NT) and untreated essential hypertension (EHT).

BACKGROUND
White-coat hypertension differs from EHT by the presence of normal ambulatory blood pressure. Sympathetic hyperactivity exists in patients with EHT in the clinical setting and is believed to contribute to the development of target organ damage. Similar organ damage has been reported in WHT, yet little is known about sympathetic neural activity in this condition.

METHODS
Using microneurography, we examined groups of 12 matched subjects with WHT, EHT and NT during the same clinical setting to quantify muscle sympathetic nerve activity as multiunit discharge (MSNA) and single units (s-MSNA).

RESULTS
The s-MSNA in WHT (54 ± 4.2 impulses/100 beats) was greater (p < 0.05) than in NT (37 ± 5.4 impulses/100 beats) despite similar age and body mass index (BMI). The EHT values of s-MSNA (73 ± 5.2 impulses/100 beats) were significantly (p < 0.05) greater than in WHT despite similar age, BMI and blood pressure levels. The MSNA followed a similar trend. White-coat hypertension had a similar cardiac baroreceptor reflex sensitivity to NT, but this was impaired in EHT relative to both NT and WHT.

CONCLUSIONS
It was shown, in the clinical setting, that central sympathetic hyperactivity exists in WHT, albeit to a lesser degree than EHT. These findings suggest that WHT may not be entirely benign and that the observed sympathetic hyperactivity may be responsible for development of target organ damage in this group of patients. (J Am Coll Cardiol 2002;40:126–32)

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White-coat hypertension (WHT) is a condition that differs from essential hypertension by the finding of a persistently elevated clinic blood pressure in the presence of normal ambulatory blood pressure values (1–4). Hyperactivity of the sympathetic nervous system, assessed directly in the clinical setting, has been implicated in the pathogenesis of essential hypertension (EHT) (5–7) and in the development of target organ damage (8,9). There has been a disagreement as to whether (10–13), or not (14–17), a similar target organ damage occurs in WHT, yet little is known about sympathetic neural activity in this condition.

Using the technique of microneurography (18,19) to quantify sympathetic discharge in the clinical setting, an increase in the mean frequency of bursts (6,7,20), representing multiunit discharge of muscle sympathetic nerve activity (MSNA) and activity from single unit (s-MSNA) discharge (21), has been reported in patients with EHT, as compared with matched normotensive subjects (NT). It has also been shown that patients with mild hypertension combined with “white-coat effect” have a reduction in MSNA during a doctor’s visit to the clinic (22). However, while that report involved patients with mild hypertension, there are no reported data available regarding such an effect in patients with WHT.

The vast majority of evidence regarding sympathetic activity in WHT has been derived indirectly from indexes such as the levels of circulating and urinary catecholamines, renin activity, insulin and heart rate variability (1,23,24). The results from these studies are variable, with daytime sympathetic activity suggested as being either increased (1,23) or normal (24).

This investigation was designed to examine whether central sympathetic vasoconstrictor output to the peripheral vascular bed is increased in the clinical setting in patients with WHT, in the same way as it is in established EHT. For this purpose, we studied matched groups of WHT and EHT in terms of age, body mass index (BMI) and blood pressure, and also a group with normal blood pressure matched for age and BMI.

METHODS
Subjects. The study involved 36 Caucasian subjects who were examined between 2000 and 2001 and in whom it was possible to identify and record single-unit activity by the technique of microneurography. They comprised 12 with newly diagnosed and untreated EHT, 12 with WHT and 12 subjects with normal blood pressure (NT). Their age ranges were 25 to 62 years, 23 to 64 years and 24 to 63 years,
respectively. All had similar occupational status (sedentary jobs) and dietary habits including a sodium intake of approximately 400 mmol/day. All patients were screened by history, physical and laboratory examination. Patients were excluded if there was evidence of arrhythmia or chronic disease that may influence the autonomic nervous system. Similarly, patients with left ventricular hypertrophy, and hypertension secondary to renal artery stenosis, phaeochromocytoma and primary hyperaldosteronism were excluded from the study.

The measured values of arterial pressure were based on the average of at least three seated recordings taken on separate occasions in the clinical setting. The groups were classified using clinic blood pressure readings according to Joint National Committee (JNC)-VI criteria (25). Normal ambulatory blood pressure was strictly defined as a daytime average of <130/80 mm Hg (11). Patients with WHT had a sustained clinic blood pressure of ≥140/90 mm Hg with a daytime ambulatory blood pressure of <130/80 mm Hg. Patients with EHT had a similar level of clinic blood pressure but ambulatory blood pressure of ≥130/80 mm Hg. Subjects with normal blood pressure had an arterial blood pressure of <130/85 mm Hg in the clinic and similar ambulatory values to the WHT group. Patients with WHT and EHT were matched for age, BMI and clinic blood pressure level, and the NT group was matched for age and BMI with the other two groups. The clinical details of the three groups are given in Table 1, and their ambulatory blood pressure data are shown in Table 2.

**General protocol.** Each subject provided informed written consent to the investigation, which was performed under the approval of the Leeds Health Authority Ethical Committee. The details of the protocol and data analysis have been published previously (21). Briefly, all the studies were performed under similar conditions between the hours of 09:00 AM and 12:00 PM, and subjects were asked to have a light breakfast and to empty their bladder before commencing the study. They were also asked to avoid nicotine and caffeine products for 12 h and alcohol and strenuous exercise for 24 h before investigation. Arterial blood pressure was measured from the arm using a standard mercury sphygmomanometer. Changes in heart rate and arterial blood pressure were monitored and recorded using a standard electrocardiogram and a Finapres device, and blood flow to the muscle of the left calf was obtained using standard venous occlusion plethysmography. Peripheral sympathetic nerve activity was recorded simultaneously by the technique of microneurography.

### Microneurography

Postganglionic muscle sympathetic nerve activity was recorded from the right peroneal nerve as previously described (18,19,21). Briefly, the neural signal was amplified (×50,000), and, for the purpose of generating bursts representing multiunit discharge, the signal was filtered (bandwidth of 700 Hz to 2,000 Hz) and integrated (time constant 0.1 s). All data were digitized at 2,000 samples/s (8 bits) except for individual action potential output, which was sampled at 12,000 samples/s.

Multiunit muscle sympathetic nerve activity was differentiated from skin sympathetic activity and afferent activity by previously accepted criteria (18,19,21). Single units (s-MSNA) were obtained from the raw action potential neurogram by adjusting the electrode position. An on-line storage oscilloscope and fast monitor sweep was used to confirm the presence of consistent action potential morphology, as previously described (21,26). Only vasoconstrictor units were accepted and examined, the criteria of acceptance being appropriate responses to spontaneous changes in arterial blood pressure, the Valsalva maneuver and isometric handgrip exercise. Measurement of calf vascular resistance (CVR) confirmed the vasoconstrictor function of the observed neural activity.

The Valsalva maneuver was performed by asking the subjects to exhale into a standard mercury manometer, at a pressure of 40 mm Hg for 15 s, while a pneumograph was observed to confirm correct performance of the test. The sympathetic activity increased during the latter part of phase II (blood pressure compensation) and/or phase III (release of strain and fall in blood pressure) and decreased during phase IV (increase and overshoot of blood pressure).

Spikes of s-MSNA were objectively counted in recordings taken over a period of at least 4 min using an electronic discriminator and were quantified as mean frequency of impulses per min and per 100 cardiac beats to avoid interference by the length of the cardiac cycle (27). The bursts of MSNA were identified by inspection when the signal-to-noise ratio was greater than 3 and were quantified in a similar manner. The variability of measuring both s-MSNA and MSNA in this laboratory did not exceed 10% (21). During the fourth phase of the Valsalva maneuver, the slope of the best linear relation between the systolic blood pressure and its pulse interval (phase 0) or the succeeding one (phase 1) was used as an indicator for cardiac baroreceptor reflex sensitivity (BRS). This noninvasive technique has been previously used to assess the gain of baroreceptor reflex control of the vagal effect on the sinoatrial node (28–31). Calf vascular resistance was obtained from the

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**Abbreviations and Acronyms**

- **BMI** = body mass index
- **BRS** = cardiac baroreceptor reflex sensitivity
- **CVR** = calf vascular resistance
- **EHT** = essential hypertension
- **IVS** = interventricular septal thickness
- **JNC** = Joint National Committee
- **LVID** = left ventricular internal diameter
- **LVMI** = left ventricular mass index
- **MSNA** = multiunit muscle sympathetic nerve activity
- **NT** = normotension
- **PW** = end-diastolic posterior wall thickness
- **s-MSNA** = single-unit muscle sympathetic nerve activity
- **WHT** = white-coat hypertension
product of mean arterial blood pressure and the mean of at least three measurements of calf blood flow during the study.

**Other procedures.** Ambulatory blood pressure monitoring was performed independently using an oscillometric device (TRACKER NIBP2, Reynolds Medical Ltd., Hertford, United Kingdom). This device has been shown (SunTech Medical Instruments, Raleigh, North Carolina) to satisfy the requirements of the Association for the Advancement of Medical Instrumentations (AAMI, Arlington, Virginia), with a difference from the reference auscultatory method of <5 ± 8 mm Hg (mean ± SD). Throughout the monitoring period, patients were asked to follow their ordinary daily activities and to go to bed not later than midnight. Blood pressure measurements were taken at half-hourly intervals during the daytime and every hour at night, to avoid patient discomfort. This frequency has been assessed in Leeds by comparing it to measurements obtained every 15 min during the day and every half-hour at night. The coefficient of variation (proportion of one SD to the mean measurement) for both systolic and diastolic pressure amounted to 6%.

Two-dimensional M-mode echocardiography (Philips SONOS 5500, Philips Medical Systems) was used to measure left ventricular dimensions in our subjects. Using American Society of Echocardiography recommendations (32), measurement of end-diastolic posterior wall thickness (PW), left ventricular internal diameter (LVID) and interventricular septal thickness (IVS) were determined and considered to represent left ventricular hypertrophy if measures of PW or IVS exceeded 11 mm. Left ventricular mass (LVM) was calculated according to the Penn convention (33) using the equation: \( LVM(g) = 1.04 \left( [(IVS + LVID + PW)^3 - (LVID)^3] - 13.6 \right) \), and, to account for body surface area, left ventricular mass index (LVMI) was derived.

**Statistics.** One-way analysis of variance with Newman-Keuls multiple post-test comparisons were used to compare the day and every half-hour at night. The coefficient of variation (proportion of one SD to the mean measurement) for both systolic and diastolic pressure amounted to 6%.

<table>
<thead>
<tr>
<th>Variables</th>
<th>NT (12)</th>
<th>WHT (12)</th>
<th>EHT (12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (women)</td>
<td>12 (6)</td>
<td>12 (8)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>46 ± 3.9</td>
<td>46 ± 4.1</td>
<td>47 ± 3.2</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>28 ± 0.8</td>
<td>28 ± 0.9</td>
<td>27 ± 0.9</td>
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<tr>
<td>Weight (kg)</td>
<td>81 ± 3.4</td>
<td>81 ± 3.5</td>
<td>78 ± 4.0</td>
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<tr>
<td>Systolic BP (mm Hg)</td>
<td>129 ± 1.7</td>
<td>157 ± 4.3</td>
<td>155 ± 3.4</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>82 ± 2.1</td>
<td>95 ± 1.1</td>
<td>93 ± 1.4</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>98 ± 2.2</td>
<td>116 ± 1.9</td>
<td>114 ± 1.3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64 ± 2.7</td>
<td>75 ± 2.4</td>
<td>66 ± 1.7</td>
</tr>
<tr>
<td>PW thickness (mm)</td>
<td>8.3 ± 0.7</td>
<td>8.7 ± 0.5</td>
<td>9.6 ± 0.2</td>
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<tr>
<td>IVS thickness (mm)</td>
<td>8.7 ± 0.3</td>
<td>8.7 ± 1.2</td>
<td>9.2 ± 0.4</td>
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<tr>
<td>LVID (mm)</td>
<td>48.3 ± 1.2</td>
<td>48.2 ± 0.9</td>
<td>47.8 ± 0.6</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>159 ± 9.5</td>
<td>164 ± 15.5</td>
<td>180 ± 3.4</td>
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<tr>
<td>LVMI (g/m²)</td>
<td>76 ± 5.0</td>
<td>83 ± 6.9</td>
<td>93 ± 2.5</td>
</tr>
</tbody>
</table>

### Table 2. Daytime and Night-Time Ambulatory Characteristics of the Three Subject Groups: NT, WHT and EHT

<table>
<thead>
<tr>
<th>Variables</th>
<th>NT vs. WHT</th>
<th>WHT vs. EHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime systolic BP (mm Hg)</td>
<td>p &gt; 0.05</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Daytime diastolic BP (mm Hg)</td>
<td>p &gt; 0.05</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Daytime MAP (mm Hg)</td>
<td>p &gt; 0.05</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Daytime heart rate (beats/min)</td>
<td>p &gt; 0.05</td>
<td>p &gt; 0.05</td>
</tr>
<tr>
<td>Night-time systolic BP (mm Hg)</td>
<td>p &gt; 0.05</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Night-time diastolic BP (mm Hg)</td>
<td>p &gt; 0.05</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Night-time MAP (mm Hg)</td>
<td>p &gt; 0.05</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Night-time heart rate (beats/min)</td>
<td>p &gt; 0.05</td>
<td>p &gt; 0.05</td>
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</tbody>
</table>

Data presented as mean ± SEM. Statistical analyses between groups (Newman-Keuls; one-way analysis of variance) are shown on the right. Abbreviations as in Table 1.
The relation between systolic blood pressure and pulse interval was examined using regression analysis. Values of $p < 0.05$ were considered statistically significant. Data are presented as mean ± SEM.

**RESULTS**

The clinical data from the three groups NT, WHT and EHT are shown in Table 1. The groups were well matched for age and BMI. There were no significant differences in echocardiographic measurements of PW, IVS and LVID and in the derived LVM and LVMI. As expected, clinic arterial blood pressure was significantly greater in EHT and WHT than in NT. Also, the heart rate was significantly higher in WHT as compared with both NT and EHT. The ambulatory blood pressure data for the groups are shown in Table 2. As anticipated, the values in EHT were significantly greater than either WHT or NT. There was no significant difference between the groups with respect to either daytime or night-time heart rate.

As can be seen in Table 3 and Figures 1 and 2, the frequency of MSNA both in terms of multiunit bursts and single-unit activity was significantly greater in WHT than in NT, but significantly smaller than that in EHT, when expressed per 100 cardiac beats. Similar findings were found when MSNA was expressed per minute, though this did not reach statistical significance between WHT and EHT, reflecting the greater heart rate in WHT. As compared with NT, single-unit discharge was 46% greater in WHT and approximately twice as much in EHT. Similar differences, although of a lesser magnitude, were seen in MSNA between the groups. A similar trend was found regarding the difference in CVR between the groups, with CVR being greatest in the EHT group. Both WHT and NT had similar BRS levels, which were significantly greater than in EHT (Table 3, Fig. 3).

<table>
<thead>
<tr>
<th>Variables</th>
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<th>WHT</th>
<th>EHT</th>
<th>Comparisons</th>
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<tr>
<td>s-MSNA (impulses/100b)</td>
<td>$37 ± 5.4$</td>
<td>$54 ± 4.2$</td>
<td>$73 ± 5.2$</td>
<td>NT vs. WHT: $p &lt; 0.05$; WHT vs. EHT: $p &lt; 0.05$</td>
</tr>
<tr>
<td>s-MSNA (impulses/min)</td>
<td>$23 ± 3.1$</td>
<td>$39 ± 3.1$</td>
<td>$47 ± 4.0$</td>
<td></td>
</tr>
<tr>
<td>MSNA (bursts/100b)</td>
<td>$34 ± 4.4$</td>
<td>$47 ± 3.8$</td>
<td>$58 ± 2.6$</td>
<td></td>
</tr>
<tr>
<td>MSNA (bursts/min)</td>
<td>$21 ± 2.6$</td>
<td>$35 ± 2.7$</td>
<td>$39 ± 2.1$</td>
<td></td>
</tr>
<tr>
<td>CVR (U)</td>
<td>$32 ± 2.4$</td>
<td>$43 ± 4.5$</td>
<td>$59 ± 2.4$</td>
<td></td>
</tr>
<tr>
<td>BRS (ms/mm Hg)</td>
<td>$6.4 ± 0.8$</td>
<td>$5.4 ± 0.8$</td>
<td>$2.6 ± 0.6$</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as mean ± SEM. Statistical analyses between groups (Newman-Keuls; one-way analysis of variance) are shown on the right.

BRS = cardiac baroreceptor reflex sensitivity; CVR = calf vascular resistance; MSNA = multiunit sympathetic nerve activity; s-MSNA = single-unit muscle sympathetic nerve activity, expressed per 100 cardiac beats (100b) and per min; other abbreviations as in Table 1.

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**Table 3. Findings in the Three Groups of Subjects: NT, WHT and EHT**

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**Figure 1.** The mean frequency of single-unit muscle sympathetic nerve activity (s-MSNA) in the three groups of subjects, NT (normotension), WHT (white-coat hypertension) and EHT (essential hypertension) expressed as mean (height of columns) and SEM (bars). Symbols represent statistical analysis between groups; *$p < 0.05$ and †$p < 0.05$.  

**Figure 2.** The mean frequency of muscle sympathetic nerve activity (MSNA) bursts in the three groups of subjects, NT (normotension), WHT (white coat hypertension) and EHT (essential hypertension) expressed as mean (height of columns) and SEM (bars). Symbols represent statistical analysis between groups; *$p < 0.05$ and †$p < 0.05$. 

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**Sympathetic Hyperactivity in White-Coat Hypertension**

JACC Vol. 40, No. 1, 2002

July 3, 2002:126–32
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DISCUSSION

Using the technique of microneurography, this investigation has shown for the first time that, in the clinical setting, WHT is associated with an increased MSNA relative to that found in subjects with normal blood pressure (NT); however, the level of sympathetic activity was not as great as that found in patients with EHT. The observed sympathetic hyperactivity in WHT could not be explained by differences in age, BMI or arterial blood pressure.

**Patient matching.** To avoid confounding factors, we only examined Caucasian subjects, as reported evidence suggests that race can affect the responses of MSNA (34). All studies were undertaken within the same environmental conditions and after a light breakfast with an empty urinary bladder, as visceral distension is known to increase sympathetic activity (35,36). The three groups were matched for age (37) and BMI (38,39). The finding that the patients with WHT had a higher heart rate than the other two groups was not unexpected, as this has previously been reported (2,3,40). In view of the known effect of blood pressure level on the magnitude of sympathetic activity in EHT (6,7,21,29), the groups with WHT and EHT were also matched for clinic blood pressure. In addition, there was no significant difference in either daytime or night-time ambulatory blood pressure between the NT and WHT groups.

**Main findings.** This study showed that sympathetic neural hyperactivity occurred in WHT and EHT, though to a lesser extent in WHT. Our findings in EHT are in keeping with previous publications confirming the presence of peripheral sympathetic hyperactivity in the clinical setting (6–9). In addition, the present study shows for the first time that peripheral sympathetic hyperactivity exists in WHT in a similar clinical environment. In a previous report involving a group of patients with mild hypertension combined with the “white-coat effect,” it was found that MSNA bursts decreased during a doctor’s visit by an average of 26% (22). Even if such a decrease in MSNA has occurred in our study, the finding of a greater MSNA in WHT than NT still supports the conclusion that sympathetic hyperactivity exists in WHT. In addition, the consideration of an increase in sympathetic output in our WHT patients is consistent with reports showing elevated plasma noradrenaline levels in WHT (23). The greater heart rate in WHT relative to NT and EHT in the clinical environment may be the result of central effects culminating in an altered balance of sympathetic and vagal effects on the sinoatrial node.

**Implications.** This study may be considered to help unravel the mechanism of sympathetic hyperactivity in WHT. The observed increase in sympathetic output occurred in both the single-unit action potentials and the multiunit bursts. The single-unit activity appears to provide a more objective and quantitative estimation of sympathetic discharge than that of multiunit bursts (21,26). In addition, as the frequency of firing of the single unit is unaffected by other recruited units, it is possible that they reflect the true central tone of the peripheral nervous system (21). The possibility of a central sympathetic activation is also consistent with our findings that the increase in sympathetic output could not be explained by known confounding factors, such as visceral reflexes or the level of arterial pressure. In addition, when WHT patients were assessed in the clinical setting, blood pressure increased beyond that observed during the daytime ambulatory monitoring. Despite this rise in blood pressure, we found an increase in efferent sympathetic output rather than a decrease, which would have been expected through intact baroreceptor reflex control. This suggests that central effects and heterogeneity of sympathetic control may have contributed to the observed sympathetic hyperactivity and the rise of arterial blood pressure. An example of such central heterogeneity has been reported during isometric exercise testing (19), when the pressor response is accompanied by an increase, rather than a reflex decrease, in MSNA.

A further implication of this study is that a possible pathogenic mechanism is suggested to account for the increased prevalence of target organ damage reported to occur in some patients with WHT, as compared with NT (10–13,23). Indeed, there are two separate findings of the present study that may be relevant. In the first instance, although evidence exists to suggest that the baroreceptor reflex control of MSNA is unaffected in EHT (29), an impairment of cardiovagal baroreceptor reflex sensitivity has also been reported in EHT (29,31), and this has been suggested to imply an adverse prognosis in cardiovascular disease (41). Our finding of a similar impairment of cardiovagal BRS in WHT and NT could be argued to suggest a favorable prognosis in WHT. Conversely, sympathetic activation is thought to be important in the development of target organ damage in subjects with EHT (8,9). Therefore,
it seems reasonable to speculate from our findings that sympathetic hyperactivity can occur in WHT, albeit on an intermittent basis, and that this may constitute one mechanism leading to the development of target organ damage. These arguments are further supported by the present finding of a slightly greater left ventricular mass in WHT and EHT as compared with NT. This occurred despite the fact that we excluded patients who were found to have obvious signs of left ventricular hypertrophy, as the latter has been shown to be associated with sympathetic hyperactivity (42). These considerations lend support to the view that WHT may not be an entirely benign condition, and could constitute an early manifestation of essential hypertension (1,12,23).

Conclusions. The present investigation has shown that WHT was associated with peripheral sympathetic hyperactivity in the clinic setting, although this was not as excessive as that seen in EHT. It is suggested that the sympathetic hyperactivity was due to central, rather than reflex, mechanisms, and this resulted in the blood pressure rise seen in WHT. The findings also support the view that WHT is not entirely innocent and may represent a prehypertensive state.

Acknowledgments
The authors thank Mr. J. Bannister, Mrs. J. Corrigan and Miss J. Hebden for their technical assistance.

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