Neurogenic Abnormalities in Masked Hypertension

Guido Grassi, Gino Seravalle, Fosca Quarti Trevano, Raffaella Dell’Oro, GianBattista Bolla, Cesare Cuspidi, Francesca Arenare, Giuseppe Mancia

Abstract—Patients with hypertension exhibit an increased sympathetic activity. No information exists as to whether this is the case in normotensive individuals in whom there is an increased ambulatory blood pressure, a condition termed “masked” hypertension. We studied 18 middle-aged subjects with masked hypertension in whom we measured muscle sympathetic nerve traffic (peroneal nerve and microneurography) and beat-to-beat arterial blood pressure at rest and during baroreceptor deactivation and activation. Measurements also included anthropometric values and insulin sensitivity (homeostasis model assessment index). Data were compared with those of 20 normotensive subjects, 18 subjects with white-coat hypertension, and 20 patients with “in-office” and “out-of-office” hypertension. All of the individuals were pharmacologically untreated and age-matched with subjects with masked hypertension. Patients with in- and out-of-office and white-coat hypertension displayed resting sympathetic nerve activity values significantly greater than normotensive subjects (75.8±2.5 and 70.8±2.2 versus 45.5±2.0 bursts per 100 heartbeats respectively; \( P<0.01 \)). This was the case also for masked hypertension (73.5±2.4 bursts per 100 heartbeats; \( P<0.01 \)), the degree of the sympathetic activation being similar for magnitude to that seen in the other 2 hypertensive conditions. Compared with normotensive subjects, baroreflex-heart rate control was significantly attenuated in all of the hypertensive states, whereas baroreflex-sympathetic control was unaffected. Homeostasis model assessment index was increased in patients with in- and out-of-office and white-coat hypertension, with a further increase in masked hypertension and a direct relation with resting sympathetic nerve traffic \( (r=0.46; \ P<0.01) \). These data provide the first evidence that masked hypertension is characterized by a marked sympathetic overdrive. They further show that the neurogenic alterations are coupled with metabolic and baroreflex abnormalities. (Hypertension. 2007;50:537-542.)

Key Words: masked hypertension ■ sympathetic activity ■ white-coat hypertension ■ ambulatory blood pressure monitoring ■ baroreflex

Measurement of efferent postganglionic muscle sympathetic nerve traffic, systemic as well as regional noradrenaline spillover, and plasma norepinephrine levels have all shown that essential hypertension is characterized by a hyperadrenergic state of which the magnitude is proportional to the disease severity.1–7 Direct and indirect measurements of sympathetic activity have additionally shown that a hyperadrenergic state can frequently be detected also in white-coat hypertension,8–10 ie, a condition in which blood pressure is increased in the clinic environment but not over the daytime.11 In contrast, no evidence exists as to whether sympathetic activity is altered when blood pressure is elevated in daily life but normal in the clinic environment, ie, a condition opposite to white-coat hypertension and termed “masked” hypertension.11 This is pathophysiologically relevant because masked hypertension has been shown to be associated with the more frequent occurrence of organ damage and cardiovascular risk,12–16 which could at least in part be ascribed to the adverse effects of a sympathetic activation.17

In the present study we addressed the above issue by comparing sympathetic nerve traffic in subjects with masked hypertension, white-coat hypertension, hypertension “in” and “out” the clinic environment, and normotension in and out the clinic environment. In each group we also measured baroreflex function and markers of insulin sensitivity to further characterize masked hypertension vis a vis the other conditions and to determine their association with the possible sympathetic alteration and thus provide information on whether they play a role in its determination.

Methods

Population

Our study was performed in middle-aged subjects of both sexes who were specifically recruited in the study if there was (1) no obesity (body mass index \( \leq 30 \text{ kg/m}^2 \)); (2) no history of smoking, excessive alcohol consumption, and major cardiovascular and noncardiovas-
cular disease, including diabetes mellitus; (3) no use of antihypertensive and other cardiovascular or metabolic drugs; (4) no echocardiographic evidence of left ventricular hypertrophy, alterations in renal function, microalbuminuria, or ultrasonographic carotid artery thickening or plaques; (5) no history or symptoms of sleep apnea syndrome; (6) no history of regular exercise habit or involvement in physical training programs; and (7) a sinus rhythm. In each subject, blood pressure was measured 3 times in the sitting position using a mercury sphygmomanometer and taking the first and fifth Korotkoff sounds to identify systolic and diastolic values, respectively. Ambulatory blood pressure was obtained over the 24-hour period using an oscillometric device (Spacelabs 90207, Spacelabs) and setting the readings at 20-minute intervals. The device was applied in the morning, and subjects were allowed to return home with the instruction to attend to their usual activities and to come back to the hospital the following day for the device removal. Based on mean office and 24-hour blood pressure values, subjects were subdivided into 4 groups: (1) normotensive subjects, ie, subjects with normal office (<140/90 mm Hg) and 24-hour (<125/79 mm Hg) blood pressure (n=20); (2) white-coat hypertensive subjects, ie, subjects with elevation in office systolic or diastolic blood pressure with normal 24-hour blood pressure (n=18); (3) masked hypertensive subjects, ie, subjects with normal office blood pressure with elevation in 24-hour systolic or diastolic blood pressure (n=18); and (4) “in-office” and “out-of-office” hypertensive subjects, ie, subjects with elevated office and 24-hour systolic or diastolic blood pressure (n=20). The cutoff blood pressure values for ambulatory blood pressure normality or elevation were those obtained in the Pressioni Arteriose Monitorate E Loro Associazioni Study. These values are similar to the cutoff values reported by other studies and mentioned by international guidelines. The study protocol was approved by the ethics committee of our institution. All of the subjects agreed to participate after being informed of the study’s nature and purpose.

Measurements

**Sympathetic Nerve Activity**

Multunit recording of different postganglionic muscle sympathetic nerve activity (MSNA) was obtained from a microelectrode inserted in a peroneal nerve posterior to the fibular head, as reported previously. Integrated nerve activity was monitored by a loudspeaker, displayed on a storage oscilloscope (model 511A, Tektronix), and recorded with blood pressure and heart rate on an ink paper. The muscle nature of a MSNA was established according to criteria described in previous studies, and recording was accepted only if the signal:noise ratio was >3. Under baseline conditions, MSNA was quantified as burst incidence over time (bursts per minute) and as bursts incidence corrected for heart rate values (bursts per 100 heartbeats). This quantification has been shown to provide reproducible values that differ only by 3.8% when assessed twice in the same session by a single investigator.

**Baroreflex**

Baroreceptor modulation of MSNA and heart rate was assessed via the vasoactive drug infusion technique. Briefly, phenylephrine was incrementally infused in an antecubital vein at doses of 0.4, 0.7, and 1.0 μg/kg per minute compared with nitroprusside at doses of 0.4, 0.7, and 1.1 μg/kg per minute. Each step was maintained for 5 minutes, and the drug initially infused was selected randomly. Mean blood pressure (diasstolic+one-third pulse pressure), MSNA, and heart rate were averaged for the 20 minutes before the infusion and the 5-minute period of each step infusion. Baroreceptor modulation of MSNA and heart rate was estimated by calculating the percentage of change in MSNA (integrated activity, ie, bursts per minute times mean burst amplitude, expressed in arbitrary units) and the absolute change in heart rate in relation to the change in mean blood pressure induced by each dose of the vasoactive drugs. In each patient, the ratio between MSNA or heart rate changes was analyzed separately for the 3-step infusions of phenylephrine and nitroprusside. Data were then further averaged to obtain MSNA- or heart rate-baroreflex sensitivity.

**Other Measurements**

Waist circumference was measured in centimeters, and body mass index was obtained by dividing body weight by the square of the height in meters. Plasma norepinephrine was measured by high performance liquid chromatography from a venous blood sample, which was used also to assess plasma glucose and insulin levels. The homeostasis model assessment (HOMA) index was obtained according to the following formula: fasting plasma glucose x fasting plasma insulin/22.5. An echocardiogram was obtained in M mode (after selection of the measurement section by a B-mode scan), which allowed left ventricular mass index to be calculated according to the Penn Convention formula. During the sympathetic nerve traffic recording and baroreflex testing, blood pressure was monitored by a finger photoplethysmographic device (Finapres 2300, Ohmeda) capable of providing accurate beat-to-beat systolic and diastolic values. Heart rate was monitored beat-to-beat by a cardiotachometer triggered by the R wave of an ECG lead.

**Protocol and Data Analysis**

The sympathetic nerve traffic study was carried out in the morning after an overnight fasting. With the subject supine, the blood sample for plasma norepinephrine, insulin, and plasma glucose determination was withdrawn. After a 30-minute interval, blood pressure, heart rate, and MSNA were continuously measured during the following: (1) an initial 20-minute baseline period, (2) the intravenous infusion of 1 vasoactive drug, (3) a 30-minute recovery period followed by a second 20-minute baseline period, and (4) the infusion of the second vasoactive drug. Data were analyzed by a single investigator unaware of the study design and of the belonging of the patients to the different groups. Individual values recorded in the baseline state or during baroreceptor manipulation were averaged for each group and expressed as mean±SEM. Comparisons between groups were made by 2-way ANOVA, using Student t test for paired or unpaired observations and Bonferroni correction for multiple comparisons to locate the statistical significance of the differences. Correlation between different variables was assessed by the Spearman analysis. P<0.05 was taken as the minimal level of statistical significance.

**Results**

As shown in the Table, the 4 groups of subjects had a similar age. Compared with normotensive subjects, patients with masked hypertension displayed a greater body mass index, waist circumference, blood glucose, HOMA index, and left ventricular mass index, all values being similar to those exhibited by patients with white-coat hypertension and in- and out-of-office hypertension, which were also elevated. Plasma norepinephrine values were not significantly different in the 4 groups. This was the case also for clinic and 24-hour mean heart rates, the only exception being an increase in office heart rate in white-coat hypertension. MSNA data are shown in Figure 1. Both when expressed as burst incidence over time and burst incidence corrected for heart rate, MSNA was markedly greater (+61.2%±6%; P<0.01) in masked hypertension than in normotension, a similar elevation characterizing white-coat hypertension and in- and out-of-office hypertension. The MSNA difference among the 3 hypertensive groups and the normotensive control subjects remained significant also when we excluded from the analysis subjects with an overweight state, ie, those with a body mass index >25 kg/m² (in- and out-of-office hypertensive subjects: 74.4±1.4 bursts per 100 heartbeats; white-coat hypertensive subjects: 64.7±2.1 bursts per 100 heartbeats; masked hypertensive subjects: 67.4±2.2 bursts per 100 heartbeats versus normotensive control subjects: 53.8±2.2.)
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Demographic and Clinic Variables in Normotensive Subjects and Subjects With White-Coat, In-Office, Out-of-Office, and Masked Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>NT (n=20)</th>
<th>WCHT (n=18)</th>
<th>EHT (n=20)</th>
<th>MHT (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.4±2.2</td>
<td>55.1±2.2</td>
<td>54.6±2.0</td>
<td>54.4±2.1</td>
</tr>
<tr>
<td>Male/female</td>
<td>13/7</td>
<td>12/6</td>
<td>14/6</td>
<td>13/5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.7±0.5</td>
<td>28.1±0.6</td>
<td>27.6±0.4</td>
<td>27.8±0.5</td>
</tr>
<tr>
<td>WC, cm</td>
<td>94.8±2.7</td>
<td>99.1±3.0</td>
<td>98.4±3.2</td>
<td>98.5±3.1</td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>117.5±2.2</td>
<td>120.3±2.3</td>
<td>136.8±2.1†</td>
<td>130.1±2.5*</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>72.0±1.5</td>
<td>75.1±1.6</td>
<td>84.3±1.8†</td>
<td>82.1±2.1†</td>
</tr>
<tr>
<td>24-h HR, b/min</td>
<td>66.9±2.0</td>
<td>70.0±2.2</td>
<td>70.5±1.8</td>
<td>69.1±2.1</td>
</tr>
<tr>
<td>Clinic SBP, mm Hg</td>
<td>122.3±2.8</td>
<td>145.5±2.9*</td>
<td>159.1±2.0†</td>
<td>128.1±2.3</td>
</tr>
<tr>
<td>Clinic DBP, mm Hg</td>
<td>78.6±2.1</td>
<td>91.4±1.9*</td>
<td>95.7±1.9†</td>
<td>82.8±2.0</td>
</tr>
<tr>
<td>Clinic HR, b/min</td>
<td>68.4±2.1</td>
<td>73.8±2.2*</td>
<td>72.2±1.9</td>
<td>70.1±2.0</td>
</tr>
<tr>
<td>Finger SBP, mm Hg</td>
<td>120.1±2.9</td>
<td>143.4±3.0*</td>
<td>157.5±2.2†</td>
<td>126.0±2.4</td>
</tr>
<tr>
<td>Finger DBP, mm Hg</td>
<td>76.2±2.3</td>
<td>89.7±2.1*</td>
<td>94.2±2.1†</td>
<td>80.9±2.1</td>
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<tr>
<td>LVMI, g/m²</td>
<td>82.4±4.9</td>
<td>98.5±5.1*</td>
<td>103.8±4.5†</td>
<td>99.8±4.9*</td>
</tr>
<tr>
<td>Plasma glucose, mmol/L</td>
<td>4.9±0.4</td>
<td>5.6±0.5</td>
<td>5.1±0.5</td>
<td>5.8±0.6</td>
</tr>
<tr>
<td>Plasma insulin, µU/mL</td>
<td>7.6±0.7</td>
<td>9.5±0.9</td>
<td>8.9±0.7</td>
<td>9.7±0.9</td>
</tr>
<tr>
<td>HOMA index, a.u.</td>
<td>1.52±0.2</td>
<td>2.36±0.3*</td>
<td>2.0±0.2*</td>
<td>2.45±0.3*</td>
</tr>
<tr>
<td>Plasma NE, pg/mL</td>
<td>208.0±13</td>
<td>237.1±23</td>
<td>249.1±19*</td>
<td>217.4±25</td>
</tr>
<tr>
<td>MSNA, bs/min</td>
<td>33.5±1.6</td>
<td>52.3±2.0†</td>
<td>57.4±2.3†</td>
<td>53.8±2.0†</td>
</tr>
<tr>
<td>MSNA, bs/100 hb</td>
<td>45.5±2.0</td>
<td>70.8±2.2†</td>
<td>75.8±2.5†</td>
<td>73.5±2.4†</td>
</tr>
</tbody>
</table>

NT indicates normotensive subjects; WCHT, subjects with white coat hypertension; EHT, subjects with in- and out-of-office hypertension; MHT, subjects with masked hypertension; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVMI, left ventricular mass index; NE, norepinephrine; bs, bursts; hb, heart beat; a.u., arbitrary unit. Data are shown as mean±SEM.

*P<0.05 and †P<0.01 refer to the statistical significance among WCHT, EHT, MHT, and NT.

First, our data offer the first evidence that masked hypertension, with an altered baroreflex sensitivity value (Figure 2, left). In all of the subjects, pooled resting MSNA values showed no relationship with the baroreflex-MSNA sensitivity (r=−0.12; P not significant), but they were directly related to HOMA index (r=0.46; P<0.01).

**Discussion**

The present study provides novel information on 2 issues. As illustrated in Figure 2, at the top, the 3 incremental doses of phenylephrine caused a progressive increase in mean blood pressure, which was accompanied by a progressive reduction in heart rate and in MSNA, whereas the 3 incremental doses of nitroprusside had opposite effects. The magnitude of the changes in MSNA induced by phenylephrine and/or nitroprusside was superimposable in the 4 groups, which, thus, showed similar values for the sensitivity of the baroreceptor-sympathetic reflex (Figure 2, right). In contrast, the concomitant heart rate changes were significantly smaller in masked hypertension, white-coat hypertension, and in- and out-of-office hypertension as compared with the true normotensive subjects, with an altered baroreflex sensitivity value (Figure 2, left).
ated with a marked sympathetic activation. They further show that this activation is of the same order of magnitude as the one characterizing in- and out-of-office hypertension, ie, the condition characterized by a blood pressure elevation both in daily life and in the clinic environment. Second, in line with previous studies, they show that white-coat hypertension is associated with an increase in sympathetic nerve traffic\textsuperscript{9} and further document that this increase is not marginal but such as to make sympathetic nerve traffic values similar to those seen in the condition characterized by in- and out-of-office hypertension. Therefore, a hyperadrenergic state should be considered as typical of masked hypertension, possibly contributing to its adverse impact on organ damage and risk of cardiovascular events.\textsuperscript{12–16} This applies also to the increased organ damage and cardiovascular risk reported in patients with white-coat hypertension,\textsuperscript{13–16,26–28} strengthening also from a pathophysiological perspective that these 2 conditions are not clinically innocent. This is further suggested by the finding that, in both instances, the degree of the adrenergic activation was similar in magnitude to the one characterizing in- and out-of-office hypertension.

The mechanisms responsible for the sympathetic activation seen in white-coat and masked hypertension have never been clarified. In the case of white-coat hypertension, a reasonable hypothesis is that this activation reflects a hyperresponsiveness to emotional and other stimuli leading to blood pressure elevations in the clinic environment.\textsuperscript{29} This, however, cannot be the case in a condition in which clinic blood pressure is normal, such as masked hypertension. Other mechanisms should thus be involved. These are unlikely to include an impairment of the baroreflex ability to restrain sympathetic nerve traffic,\textsuperscript{3,17} because in subjects with masked hypertension, modulation of sympathetic activity by baroreceptor stimulation and unloading was unimpaired, with no relationship between overall baroreflex sensitivity and baseline sympathetic drive. A more likely hypothesis is that the sympathetic activation depends on the circulating angiotensin II concentrations, given the evidence that angiotensin II exerts central and peripheral excitatory effects on sympathetic neural outflow.\textsuperscript{30} Another hypothesis is that the hyperinsulinemic state originating from a reduced insulin sensitivity is involved because of the well known ability of insulin to increase sympathetic nerve activity, particularly to skeletal muscle tissue,\textsuperscript{31–33} and the evidence that, in our masked hypertensive subjects, the HOMA index was increased compared with the values seen in normotensive subjects. It should be emphasized that this explanation applies also to white-coat hypertension, of which the sympathetic activation was associated with no MSNA-baroreflex blunting but with an increased HOMA index. It should also be emphasized that this offers another pathophysiologic element in favor of the similarity of these 2 conditions to in- and out-of-office hypertension, in which baroreflex control of sympathetic activity has also been shown to be normal with a concomitant frequent derangement in glucose metabolism.\textsuperscript{34}

A few other points deserve to be discussed. At first glance it may paradoxically appear that, in our population, sympathetic activation may be associated with either elevated (in- and out-of-office hypertension and white-coat hypertension) or normal (masked hypertension) clinic blood pressure values. This paradox, however, is more apparent than real, given the evidence that, in our patients with masked hypertension, clinic blood pressure was somewhat greater than in truly normotensive subjects, similar to what we observed for ambulatory blood pressure values in subjects with white-coat hypertension. This finding, which is in line with the results of a Pressioni Arteriose Monitorate E Loro Associazioni Study,\textsuperscript{15} suggests that sympathetic activity is increased when...
blood pressure is elevated independently on the relative degree of elevation between different blood pressure measurements. Second, at variance from sympathetic nerve traffic, plasma norepinephrine did not differ significantly in the 4 groups of subjects of our study. This offers a further example of the reduced ability of this variable to detect in a sensitive fashion between-group differences in sympathetic drive.1,15 Three, compared with truly normotensive subjects, clinic and 24-hour heart rate showed a tendency to be greater in white-coat, masked, and in- and out-of-office hypertension. This may originate from the reduced baroreflex ability to modulate heart rate seen in all 3 of the groups. It may also originate, however, from the reduced inhibitory effects exerted by the vagus on sinus node reported in hypertension.22 However, the heart rate differences were small and with 1 exception not statistically significant. This may mean that, because of the multiple factors involved in its modulation, heart rate is a less specific marker of sympathetic drive even when averaged over the 24 hours.36 It may also mean, however, that the sympathetic activation typical of such hypertensive states is qualitatively and/or quantitatively different at cardiac and peripheral levels, as has been reported in a number of cardiovascular diseases.37,38

Perspectives

The findings of the present study have both clinical and methodologic implications. From a clinical viewpoint, they suggest that the antihypertensive approach of masked hypertension should be based on drugs capable of favorably interfering with the sympathetic and the metabolic dysfunction. From a methodologic viewpoint, they provide some insights for studies comparing sympathetic nerve traffic in hypertensive and normotensive individuals. That is, if the diagnosis of normotension is not established also by ambulatory blood pressure criteria, individuals with masked hypertension may be included in the control group with higher “control” nerve traffic values and minimization of the actual differences with the pathophysiologic states.

Disclosures

None.

References

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