The Frequency of Combined Target Organ Damage and the Beneficial Effect of Ambulatory Blood Pressure Monitoring in Never Treated Mild-to-Moderate Hypertensive Patients

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SUMMARY

The aim of this study was to determine the frequency of target organ damage (TOD) and the beneficial properties of ambulatory blood pressure monitoring (ABPM) for detecting patients who are at high risk for TOD and cardiovascular disease in never treated mild-to-moderate hypertension.

Sixty-seven patients (28 males and 39 females, mean age, 49.6 ± 9.5 years) were divided into two groups, dippers (group I, n = 43) and nondippers (group II, n = 24), according to nocturnal blood pressure (BP) reduction of less than 10%. The groups were compared with respect to demographic and laboratory data and the signs of TOD (microalbuminuria, left ventricular hypertrophy, and retinopathy). We also tested the relationship between ABPM and clinic BP findings with TOD. Group I had significantly lower values than group II for serum fibrinogen (0.28 ± 0.06 versus 0.32 ± 0.06 g/L, P = 0.02), uric acid (0.18 ± 0.05 versus 0.25 ± 0.11 mmol/L, P = 0.01), urinary sodium excretion (133.7 ± 45.2 versus 161.8 ± 52.2 mmol/L, P = 0.02), urinary albumin excretion (17.5 ± 14.2 versus 31.3 ± 19.7 mg/24-h, P = 0.001), left ventricular mass index (111.8 ± 31.0 versus 128.7 ± 36.6 g/m2, P = 0.05), and the prevalence of hypertensive retinopathy (51% versus 83%, P = 0.01). The frequency of the combination of all three signs of TOD (microalbuminuria, left ventricular hypertrophy, and hypertensive retinopathy) was higher in nondippers than in dippers (71.4% versus 30%, P = 0.04). We suggest ABPM may provide clinical information to detect patients prone to develop cardiovascular risks and TOD in newly diagnosed mild-to-moderate hypertension. (Int Heart J 2005; 46: 1073-1082)

Key words: Ambulatory blood pressure monitoring, Essential hypertension, Hypertensive retinopathy, Left ventricular hypertrophy, Microalbuminuria, Target organ damage

ESSENTIAL hypertension is a major risk factor for coronary artery disease, cerebrovascular disease, retinopathy, and nephropathy. Most patients with essen-

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tial hypertension are unaware of their high blood pressure (BP) for a long time so that a large number of hypertensive patients have target organ damage (TOD) when first admitted to hospital.\textsuperscript{1)}

The Seventh Report of the Joint National Committee and British Hypertension Society Guideline recommend limiting the number of routine investigations to the first evaluation of uncomplicated hypertensive patients. Therefore, echocardiography and detection of urinary albumin excretion are not required routinely in mild-to-moderate essential hypertension.\textsuperscript{2,3)}

Ambulatory blood pressure monitoring (ABPM) is a more valuable technique with which to determine hypertensive TOD and cardiovascular events than clinical BP readings.\textsuperscript{4)} Previous studies have shown that adverse effects of hypertension such as left ventricular hypertrophy, retinopathy, and nephropathy are better related to ABPM than clinical BP readings.\textsuperscript{5-7)} In addition, ABPM also provides information for detecting increased hemodynamic load and abnormal circadian BP variations. Data from the literature have shown the existence of an association between decreased BP fall at nighttime and TOD in hypertension.\textsuperscript{8)} However, the use of ABPM is limited to some specific circumstances such as for evaluation of unusual BP variability, possible white-coat hypertension, drug-resistant hypertension, symptomatic hypotension with antihypertensive medications, and determining the efficacy of drug treatment over 24 hours.\textsuperscript{2,3)}

The routine use of ABPM in newly diagnosed mild-to-moderate hypertensive patients has not been recommended yet. The aim of this study was to determine the frequency of TOD and the beneficial effect ABPM for detecting patients who are at high risk for TOD and cardiovascular disease in never treated mild-to-moderate hypertension.

\section*{METHODS}

The cohort observation study included 67 patients (28 men and 39 women, mean age, $49.6 \pm 9.5$ years) with untreated, newly diagnosed mild or moderate essential hypertension. The exclusion criteria were severe hypertension (BP higher than $> 160/100$ mmHg), patients taking antihypertensive therapy, secondary hypertension, diabetes mellitus, renal failure with creatinine clearance less than $30 \text{ mL/min/1.73 m}^2$ body surface area, pregnancy, coronary artery disease, body mass index (BMI) $> 32 \text{ kg/m}^2$, and macroalbuminuria. All patients were questioned about their family history of hypertension and their personal smoking habits. Weight and height were measured by standard techniques and body mass index (BMI) was calculated in kilograms per meter squared.

The ethics committee approved the study and all participants provided informed consent for all procedures in the study protocol.
Blood pressure was measured by a mercury sphygmomanometer after the patient had been in a sitting position for 5 minutes. For each subject, we recorded the average of three readings obtained within 5 minutes. Hypertension was defined as systolic BP \( \geq 140 \) mmHg and diastolic BP \( \geq 90 \) mmHg, as recommended in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII reports).2)

ABPM was performed using a portable, noninvasive Suntech 104 Accu-tracker II device. Blood pressure readings were taken automatically at 15-minute intervals during the day (9:00 AM to 10:00 PM) and 30-minute intervals during the night (10:00 PM to 9:00 AM). All patients were encouraged to carry out their normal daily routine activities during the ABP recording and to complete a diary card documenting their actual awake and asleep times. Patients were asked to define the quality of their sleep and only those who reported a normal sleep were included in the study. The following parameters were recorded for each patient: 24-hour mean systolic and diastolic BP, mean daytime systolic and diastolic BP, and mean nighttime systolic and diastolic BP. Systolic BP load was defined as the percentage of readings greater than 140 mmHg, and diastolic BP load was greater than 90 mmHg during a 24-hour period. Individuals who exhibited a nocturnal BP reduction of higher than 10% from their average daytime systolic BP and diastolic BP were considered as dippers (group I). The rest were classified as nondippers (group II).

A fasting blood sample was collected from each patient and analyzed for serum levels of glucose, creatinine, uric acid, hemoglobin, fibrinogen, and serum lipid profile. A 24-hour urine sample was also obtained, and daily urinary sodium excretion (UNaE), creatinine clearance rate, and urinary albumin excretion (UAE) were investigated. Urinary albumin excretion greater than 30 mg/24 hours was defined as microalbuminuria. Microalbuminuria was detected in 24-hour urine samples by radioimmunoassay.

Each subject underwent direct funduscopic examination for assessment of possible retinopathy. The same ophthalmologist performed all these examinations, and was blinded to the patients' BP levels at the time. Lesions were divided into two groups of retinopathy findings (presence or absence) according to the Keith-Wagener classification.9)

Each individual also underwent cardiac ultrasound. Tracings were recorded under 2-dimensional guidance, and measurements were taken at the tip of the mitral valve or just below that point. Left ventricular measurements were performed at end diastole and end systole according to the recommendations of the American Society of Echocardiography.10) An Acuson 128XP 10/C color-Doppler ultrasound imager with a 2.5-5 MHz transducer was used. Left ventricular mass was calculated using the formula devised by Devereux, et al.11) Left ventric-
ular mass index (LVMI) was calculated by dividing left ventricular mass by body surface area in g/m².

Groups I and II were compared with respect to age, sex distribution, smoking habit, family history of hypertension, BMI, serum levels of glucose, creatinine, uric acid, hemoglobin, and fibrinogen, serum lipid profile, UNaE, creatinine clearance rate, microalbuminuria, LVMI, and fundus findings. We also tested the relationship between clinical BP findings and TOD, and between ABPM findings and TOD.

**Statistical analysis:** The program SPSS for Windows, version 10.0 (SPSS Inc., Chicago, IL, USA) was used to perform the statistical calculations. Data are expressed as the mean ± standard deviation. Student's t-test and the chi-square test were used to compare the findings between the two groups. A P < 0.05 was considered to indicate statistical significance.

**RESULTS**

According to the ABPM records of the 67 patients, 43 (64%) subjects were classified as dippers (group I) and 24 (36%) as nondippers (group II). There were no significant differences between groups I and II with respect to age, sex distribution, mean BMI, number of smokers, or positive family history of hypertension.

Group I had significantly lower values than group II for serum fibrinogen

<p>| Table 1. Physical Characteristics, Laboratory Findings, and Indicators of Target Organ Damage in Dipper and Nondipper Hypertensive Patients |
|---------------------------------|-----------------|-----------------|-----|</p>
<table>
<thead>
<tr>
<th></th>
<th>Dippers (n= 43)</th>
<th>Nondippers (n= 24)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.6 ± 9.9</td>
<td>49.6 ± 9.0</td>
<td>0.98</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>16/27</td>
<td>12/12</td>
<td>0.43</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.7 ± 4.0</td>
<td>30.6 ± 4.0</td>
<td>0.93</td>
</tr>
<tr>
<td>Smokers (No. [%])</td>
<td>10 (23%)</td>
<td>8 (33%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Family history of EH (No. [%])</td>
<td>18 (42%)</td>
<td>14 (58%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.1 ± 0.4</td>
<td>5.0 ± 1.0</td>
<td>0.52</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>86.8 ± 21.3</td>
<td>80.8 ± 22.1</td>
<td>0.26</td>
</tr>
<tr>
<td>Uric acid (mmol/L)</td>
<td>0.18 ± 0.05</td>
<td>0.25 ± 0.11</td>
<td>0.01*</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>4.3±1.9</td>
<td>3.2±0.9</td>
<td>0.01*</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>0.28 ± 0.06</td>
<td>0.32 ± 0.06</td>
<td>0.02*</td>
</tr>
<tr>
<td>UNaE (mmol/L)</td>
<td>133.7 ± 45.2</td>
<td>161.8 ± 52.2</td>
<td>0.02*</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>111.8 ± 31.0</td>
<td>128.8 ± 36.6</td>
<td>0.05*</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>80.2 ± 22.3</td>
<td>83.4 ± 17.9</td>
<td>0.54</td>
</tr>
<tr>
<td>Urine albumin excretion (mg/24-h)</td>
<td>17.5 ± 14.2</td>
<td>31.3 ± 19.7</td>
<td>0.001**</td>
</tr>
<tr>
<td>Retinopathy (No. [%])</td>
<td>22 (51%)</td>
<td>20 (83%)</td>
<td>0.01*</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; EH, essential hypertension; LDL, low-density lipoprotein; and LVMI, left ventricular mass index. *P < 0.05, **P < 0.001
(0.28 ± 0.06 versus 0.32 ± 0.06 g/L, \(P = 0.02\)), uric acid (0.18 ± 0.05 versus 0.25 ± 0.11 mmo/L, respectively, \(P = 0.01\)), UNaE (133.7 ± 45.2 versus 161.8 ± 52.2 mmol/L, respectively, \(P = 0.02\)), UAE (17.5 ± 14.2 versus 31.3 ± 19.7 mg/24-h, respectively, \(P = 0.001\)), LVMI (111.8 ± 31.0 versus 128.7 ± 36.6 g/m², respectively, \(P = 0.05\)), and prevalence of hypertensive retinopathy (51% versus 83%, respectively, \(P = 0.01\)) (Table I).

Both groups registered similar values for systolic BP (151.4 ± 11.1 versus 155.4 ± 6.9 mmHg) and diastolic BP (95.2 ± 8.2 versus 96.8 ± 5.8 mmHg, \(P > 0.05\)), but 24-hour systolic BP (141.7 ± 7.5 versus 146.3 ± 11.1 mmHg, respectively, \(P = 0.04\)), 24-hour diastolic BP (90.0 ± 7.2 versus 87.6 ± 8.5 mmHg, respectively, \(P = 0.02\)), nighttime systolic BP (133.8 ± 7.4 versus 139.0 ± 10.8 mmHg, respectively, \(P = 0.02\)), nighttime diastolic BP (76.7 ± 8.1 versus 84.4 ±

### Table II. Comparison of Clinic and Ambulatory Blood Pressure Findings in Dipper and Nondipper Hypertensive Patients

<table>
<thead>
<tr>
<th></th>
<th>Dippers (n = 43)</th>
<th>Nondippers (n = 24)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic systolic BP (mmHg)</td>
<td>151.4 ± 11.1</td>
<td>155.4 ± 6.9</td>
<td>0.12</td>
</tr>
<tr>
<td>Clinic diastolic BP (mmHg)</td>
<td>95.2 ± 8.2</td>
<td>96.8 ± 5.8</td>
<td>0.56</td>
</tr>
<tr>
<td>24-h systolic BP (mmHg)</td>
<td>141.7 ± 7.5</td>
<td>146.3 ± 11.1</td>
<td>0.04*</td>
</tr>
<tr>
<td>24-h diastolic BP (mmHg)</td>
<td>83.0 ± 7.1</td>
<td>87.6 ± 8.5</td>
<td>0.02*</td>
</tr>
<tr>
<td>Daytime systolic BP (mmHg)</td>
<td>148.8 ± 8.1</td>
<td>153.6 ± 12.8</td>
<td>0.07</td>
</tr>
<tr>
<td>Daytime diastolic BP (mmHg)</td>
<td>90.0 ± 7.2</td>
<td>89.2 ± 7.2</td>
<td>0.70</td>
</tr>
<tr>
<td>Nighttime systolic BP (mmHg)</td>
<td>133.8 ± 7.4</td>
<td>139.0 ± 10.8</td>
<td>0.02*</td>
</tr>
<tr>
<td>Nighttime diastolic BP (mmHg)</td>
<td>76.7 ± 8.1</td>
<td>84.4 ± 9.1</td>
<td>0.001**</td>
</tr>
<tr>
<td>24-h systolic BP load (%)</td>
<td>44.5 ± 11.2</td>
<td>58.2 ± 20.7</td>
<td>0.001**</td>
</tr>
<tr>
<td>24-h diastolic BP load (%)</td>
<td>27.8 ± 12.4</td>
<td>39.7 ± 16.4</td>
<td>0.006*</td>
</tr>
</tbody>
</table>

BP indicates blood pressure. *\(P < 0.05\), **\(P < 0.001\)

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**Figure 1.** Intersection distribution of patients with microalbuminuria, retinopathy, and left ventricular hypertrophy (\(n = 51\) patients).
9.1 mmHg, respectively, \( P = 0.001 \), systolic BP (44.5 ± 11.2% versus 58.2 ± 20.7%, respectively, \( P = 0.001 \)), and diastolic BP load (27.8 ± 12.4% versus 39.7 ± 16.4%, respectively, \( P = 0.001 \)) were lower in dippers than in nondippers (Table II).

Fifty-one patients had at least one of three signs of TOD (microalbuminuria, retinopathy, and left ventricular hypertrophy). Of these 51 patients, 24 (47%) exhibited all three TOD signs together. The percentage distribution of association of microalbuminuria, retinopathy, and left ventricular hypertrophy is shown in Figure 1. The frequency of the combination of all three signs was higher in nondippers than in dippers (71.4% versus 30%, respectively; \( P = 0.04 \)) (Figures 2 and 3).
DISCUSSION

The results of the present study indicate that the frequency of combined target organ damage is as high as 47% in newly diagnosed mild-to-moderate hypertensive patients. The exact prevalence of combined TOD in these patients is not well established. The high frequency of TOD underlines that most patients with essential hypertension may not be aware of their high BP for a long time, and therefore, that a large number of patients have hypertensive target organ damage when they are first admitted to hospital. Therefore, in addition to assessing the degree of BP elevation, it is also very important to do a thorough work-up for TOD in untreated newly diagnosed mild-to-moderate hypertensive patients.

Another cause of the high frequency of TOD can be explained by the large number of obese patients in our study. Obesity is a well known modifiable risk factor for essential hypertension and it is associated with both increased left ventricular mass and microalbuminuria in hypertensive patients. These findings suggest that weight reduction remains a crucial component of the therapeutic strategy to ameliorate hypertension and TOD in essential hypertension.

Although the use of ABPM in uncomplicated essential hypertension is limited only in some specific conditions, it provides more information to assess daily BP load and BP variations. In our study, we found that the evidence of TOD correlated with 24-hour BP, whereas they were not significantly correlated with clinical BP findings. A previous study reported that ABPM findings are more closely related to evidence of hypertensive end-organ damage than with clinical readings in essential hypertension. In line with earlier findings, our results indicate that ABPM gives a more sensitive assessment of TOD than clinical BP readings.

Another finding of our study was that the combination of three signs of TOD was significantly more frequent in nondippers than in dippers. Some, but not all, series have reported that among patients with uncomplicated essential hypertension, an absent or blunted nocturnal fall in BP is associated with a higher risk of left ventricular hypertrophy, silent cerebrovascular disease, microalbuminuria, and progression of renal damage. There is no definitive consensus about whether the TOD in nondipper hypertensive subjects is a result of the absence of a nocturnal BP decrease or the greater hemodynamic load in this setting. In the present study, the increased daily BP load in nondipper hypertensives suggests that both the absence of a nocturnal BP decrease and greater hemodynamic load may have caused the high TOD rate in nondippers.

In our study, we found that elevated serum uric acid and fibrinogen levels were associated with the absence of the normal circadian BP variation. Several previous studies have revealed that elevated uric acid and fibrinogen levels are associated with an increased risk of cardiovascular disease and TOD in hypertensive patients. The pathogenetic roles of fibrinogen and uric acid in the devel-
Development of hypertensive complications have been suggested to be due to endothelial dysfunction, increased platelet adhesiveness, and aggregation. In our study, exposure to the increased BP load and elevated uric acid and fibrinogen levels may have led to endothelial damage in nondipper hypertensive patients.

Clinical and experimental studies have revealed that hypertensive TOD is strongly correlated with salt intake, and this identifies salt intake as a potential marker of susceptibility to hypertensive complications. In our study, urinary sodium excretion was significantly higher in nondipper than in dipper patients.

Microalbuminuria, a well-recognized marker for adverse cardiovascular outcomes in population-based studies, has been associated with other TOD in hypertensive subjects. A previous study has also shown that increased urinary albumin excretion is associated with left ventricular hypertrophy, coronary artery disease, and myocardial ischemia. In line with this, we found that the microalbuminuria of our essential hypertensive patients was correlated with both left ventricular hypertrophy and retinopathy. These results are in line with reports by Calvino, et al and Cerasola, et al and we suggest that microalbuminuria may be a marker of endothelial damage throughout the entire vascular system.

The main limitation in our study was the patients were diagnosed as dipper or nondipper based on a single 24-hour ABPM. Some studies have revealed that classifying patients as dippers or nondippers based on a single ABP recording is likely to be unreliable. However, we excluded patients with sleeping disorders and those who reported in their diaries variations in their daily activities so the risks of false positive and negative records were reduced.

In conclusion, the evidence for TOD was found to be more than expected in never treated hypertensive patients in our study. Additionally, circadian BP variation and BP load, which are detected with ABPM, are associated with TOD and cardiovascular risk factors. The high frequency of TOD in nondippers suggests the potential utility of APBM may became widespread in patients with newly diagnosed mild-to-moderate essential hypertension, for the detection of patients who have cardiovascular risks, and predicts TOD.

REFERENCES


