Adiponectin, Insulin Resistance, and Left Ventricular Structure in Dipper and Nondipper Essential Hypertensive Patients

Paolo Della Mea, Mario Lupia, Valentina Bandolin, Samuele Guzzon, Nicoletta Sonino, Roberto Vettor, and Francesco Fallo

Background: Adiponectin is an adipocyte-derived protein with insulin-sensitizing and antiatherogenic properties. Failure to decrease blood pressure (BP) normally during night in hypertensive patients has been independently associated with left ventricular hypertrophy.

Methods: We examined the relationship between adiponectin levels, insulin sensitivity, and left ventricular structure in 40 newly diagnosed never-treated patients with essential hypertension, including 20 patients with a normal night-time pressure decrease (ie, dippers) and 20 patients with BP persistently elevated throughout the 24-h period (ie, nondippers). All subjects had grade 1–2 hypertension, aged 18 to 65 years, no diabetes mellitus, no obesity, no hyperlipidemia, and no cardiopulmonary, renal, or hepatic disease.

Results: The two groups of patients were similar for age, sex, body mass index, and had no differences for clinic, 24-h, and diurnal BP, and 24-h, diurnal, and nocturnal heart rate, as well as glucose, total cholesterol, and triglyceride levels. Plasma insulin and homeostasis model assessment (HOMA index) were higher ($P < .01$), and adiponectin levels were lower ($P < .005$) in nondippers than in dippers. Adiponectin correlated inversely with HOMA index and insulin levels ($r = -0.58$, and $r = -0.62$, respectively, $P < .001$) in the entire population. Nondippers showed left ventricular mass, relative wall thickness, and measure of early and late diastolic peak flow velocity ratio similar to those of dippers.

Conclusions: In the absence of major cardiovascular risk factors, nondipper essential hypertensive patients show more prominent insulin resistance and lower adiponectin compared to dippers. Therapeutic modulation of adiponectin or insulin resistance might provide additional benefit to the conventional antihypertensive treatment.

Essential hypertension is referred to as an insulin-resistant state in humans, even in the absence of other metabolic abnormalities, and insulin resistance may contribute to the cardiovascular risk in this disorder. Adiponectin is a novel adipose tissue-derived protein, with an important role in regulating energy homeostasis, ameliorating insulin sensitivity, and preventing atherogenesis. In human cross-sectional studies, plasma adiponectin levels are negatively correlated with obesity and waist–hip ratio, diabetic dyslipidemia, insulin resistance, and cardiovascular disease. A negative correlation between adiponectin and blood pressure (BP) levels has been observed in normotensive populations. Results of recent studies on adiponectin in hypertension have been inconsistent. High, low, or normal adiponectin levels (only in patients without insulin resistance) are reported in patients with essential hypertension. Failure to decrease BP during the night is independently associated with an increase in left ventricular (LV) mass and with glucose intolerance in patients with essential hypertension. No information is available on the relation of adiponectin levels with BP profile and cardiac mass. The purpose of this study was to examine the relationship between adiponectin levels, insulin resistance, and BP profile in patients with a normal nocturnal BP decrease (ie, dip-


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0895-7061/05/$30.00 © 2005 by the American Journal of Hypertension, Ltd.
Published by Elsevier Inc.
doi:10.1016/j.amjhyper.2004.08.029

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pers) and those with BP persistently elevated throughout the 24-h period (ie, nondippers).

Methods
Patients
In this prospective study, 40 newly diagnosed never-treated patients with essential hypertension, including 20 patients with a normal nighttime pressure decrease (ie, dippers), and 20 patients with BP persistently elevated throughout the 24-h period (ie, nondippers), were considered. Within a larger population seen at our outpatients clinic during the past 2 years, these patients were consecutively selected according to the following criteria: 1) grade 1–2 hypertension, according to World Health Organization–International Society of Hypertension (WHO–ISH) guidelines, with clinic BP ≥140/90 mm Hg measured by mercury sphygmomanometer in a sitting position in at least three separate casual measurements within the past month15; 2) age 18 to 65 years; 3) no obesity (ie, body mass index [BMI] ≥30 kg/m217); no hyperlipidemia (ie, total serum cholesterol ≥5.8 mmol/L or serum triglycerides ≥1.7 mmol/L); no smoking habit (ie, at least one cigarette daily for 1 year within the past 5 years); 4) no clinical or laboratory evidence of cardiopulmonary, renal, or hepatic disease. In all patients, duration of hypertension was <1 year. Duration of disease was obtained by careful investigation of the patient’s history and from family practitioner records. Secondary hypertension was excluded on the basis of standard biochemical, hormonal, and instrumental tests. Each subject provided informed consent for the study, which was approved by the institutional Ethics Committee.

BP and Heart Rate Monitoring
On a day other than the follow-up office visit, all hypertensive patients underwent 24-h ambulatory BP monitoring (ABPM) using the Takeda TM24300 (Asahi, Japan) monitor. Recording started between 30 AM and 9 AM. Patients were instructed to closely report daily activities during the recordings. Recording was programmed for every 15 min during a 24-h period. Measured values of systolic BP, diastolic BP, and heart rate were stored in digital memory. The readings of the automatic recorder were checked against those obtained with a mercury sphygmomanometer at the beginning and the end of each 24-h monitoring session; a difference of ±5 mm Hg was considered an adequate agreement between the two methods. Measured values of systolic BP, diastolic BP, and heart rate were downloaded from the monitor to an IBM PC (IBM Co., New York, NY) using custom software. Blood pressure and heart rate measurements were excluded from the analysis when they were missing or labeled as technically erroneous by the monitor software. In particular, systolic BP values >240 or <70 mm Hg, and diastolic BP values >140 or <40 mm Hg were not included. If a BP recording had less than 70% successful readings, it was rejected and repeated. During the monitoring, a written diary of physical and mental activities was kept, and patients were invited to report the sleep span. Blood pressure readings of patients with sleep disturbances were discarded (patients not included in the study). Daytime and night-time were considered as the intervals from 8 AM to 10 PM and from midnight to 6 AM, respectively. Blood pressure dipping was defined as a night-to-day systolic and diastolic decrease ≥10%18–20. In accordance with this definition, 20 patients were dippers and 20 patients were nondippers.

Echocardiographic Examination
Echocardiography was performed by standardized procedures with a SONOS 4500 (Hewlett Packard, HP Co., Palo Alto, CA) echo machine. The echocardiographic study protocol recorded at least 10 cycles of two-dimensional parasternal long- and short-axis LV views with optimal orientation of the M-mode cursor beam. The LV internal dimensions, interventricular septum, and posterior wall thickness were measured according to the recommendations of the American Society of Echocardiography.21 End-diastolic relative wall thickness (RWT) (ie, the ratio of posterior wall thickness to one-half LV internal dimensions) was calculated as the index of LV geometric pattern. Values >0.44 were considered to indicate LV concentric geometry.22 The Penn convention was used to calculate LV mass by an anatomically validated formula.23 The LV mass was indexed by body height to the 2.7 power (LV mass/height2.7) to correct the effect of overweight, and the partition value of 51 g/m2.7 was used to define LV hypertrophy in both genders.24 Left ventricular mass normalized for body surface area (LV mass/BSA) was also calculated as g/m2.

In all patients pulsed Doppler recordings at the level of the mitral valve tips from apical four-chambers two-dimensional views were obtained to measure early (E) and late (A) diastolic peak flow velocities, their ratio (E/A ratio), and E-wave deceleration time, as measurement of diastolic filling.25 Diastolic dysfunction was defined as E/A ratio <1.

One reader (ML), unaware of the patient’s or control’s identity, performed all echocardiographic and Doppler measurements.

Laboratory Studies
In all subjects, biochemical and endocrine–metabolic profile were obtained after overnight fasting at 8 AM, during routine blood testing at the time of 24-h ABPM. Insulin sensitivity was calculated according to the formula of the homeostasis model assessment (HOMA index): insulin resistance = fasting plasma insulin (µU/mL) × fasting plasma glucose (mmol/L)/22.5.26 The index is highly correlated with the insulin
resistance index assessed by the euglycemic–hyperinsulinemic clamp, which is the gold standard of insulin resistance measurement, and is widely adopted in clinical studies for subjects with various degree of insulin sensitivity, including hypertensive subjects. Plasma insulin levels were measured by radioimmunoassay (RIA) using a commercially available kit (Behring, Scoppito, Italy) (normal range, 43 to 172 mmol/L). Plasma adiponectin was measured by a specific RIA obtained from Linco Research, Inc. (St. Charles, MO), with minor modifications, as previously described. Recombinant human adiponectin was used as standard, and a multispecies adiponectin rabbit antiserum was used. The assay buffer contained 10.0 mmol phosphate buffer at pH 7.6, sodium azide (0.09%), and BSA (0.15%). Normal controls (\(n = 20\)) were 28.1 \(\pm\) 10.5 \(\mu\)g/mL. For hormone measurements, intra-assay and interassay coefficients of variation were <10%. All other biochemical variables were assayed in the same laboratory using standard methods.

### Statistical Analysis

All group data are reported as means \(\pm\) SD. Statistical significance between groups was assessed by Student t test for independent samples. The \(\chi^2\) statistics was used to assess differences between categorical variables. Pearson’s correlation coefficient was calculated to test for a correlation between two variables for the entire population. A \(P < .05\) was considered statistically significant. All analyses were carried out with the SYSTAT 10.0 (Systat Software GmbH, Erkrah, Germany) statistical package.

### Results

#### Characteristics of the Study Participants

Clinical, endocrine, and metabolic parameters of dipper and nondipper subjects in this study are shown in Tables 1 and 2. The two groups of patients were similar for age, sex, BMI, and had no statistical differences for clinic, 24-h, and diurnal BP, 24-h, diurnal, and nocturnal heart rate. Also, the dipper group did not differ significantly in fasting glucose, total cholesterol, and triglyceride levels from the nondipper group. At variance, plasma adiponectin and HOMA index were higher in nondippers than in dippers. Adiponectin correlated inversely with HOMA index and insulin levels (\(P < .005\)) in nondippers than in dippers. Adiponectin correlated inversely with HOMA index and insulin levels (\(n = 40, r = -0.58,\) and \(r = -0.62,\) respectively, \(P < .001\)). No correlation

### Table 1. Demographic and metabolic characteristics of the study groups

<table>
<thead>
<tr>
<th></th>
<th>Dippers</th>
<th>Nondippers</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.4 (\pm) 13.2</td>
<td>53.0 (\pm) 14.0</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>8/12</td>
<td>6/14</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>26.5 (\pm) 3.1</td>
<td>26.3 (\pm) 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.4 (\pm) 0.7</td>
<td>5.4 (\pm) 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>65.2 (\pm) 23.6</td>
<td>92.4 (\pm) 38.2</td>
<td>(&lt; .005)</td>
</tr>
<tr>
<td>HOMA index</td>
<td>2.3 (\pm) 0.9</td>
<td>3.3 (\pm) 1.4</td>
<td>(&lt; .01)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.0 (\pm) 0.4</td>
<td>5.1 (\pm) 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.1 (\pm) 0.4</td>
<td>1.2 (\pm) 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Adiponectin ((\mu)g/mL)</td>
<td>23.5 (\pm) 10.1</td>
<td>13.4 (\pm) 6.7</td>
<td>(&lt; .005)</td>
</tr>
</tbody>
</table>

Mean values \(\pm\) SD.

### Table 2. Clinic and ambulatory blood pressure and heart rate of the study groups

<table>
<thead>
<tr>
<th></th>
<th>Dippers</th>
<th>Nondippers</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic systolic BP (mm Hg)</td>
<td>148.5 (\pm) 14.0</td>
<td>151.7 (\pm) 8.2</td>
<td>NS</td>
</tr>
<tr>
<td>Clinic diastolic BP (mm Hg)</td>
<td>97.5 (\pm) 10.9</td>
<td>95.8 (\pm) 6.9</td>
<td>NS</td>
</tr>
<tr>
<td>Clinic heart rate (beats/min)</td>
<td>75.9 (\pm) 9.0</td>
<td>73.5 (\pm) 7.2</td>
<td>NS</td>
</tr>
<tr>
<td>24-h systolic BP (mm Hg)</td>
<td>139.0 (\pm) 11.5</td>
<td>145.1 (\pm) 13.3</td>
<td>NS</td>
</tr>
<tr>
<td>24-h diastolic BP (mm Hg)</td>
<td>85.8 (\pm) 8.6</td>
<td>84.8 (\pm) 10.3</td>
<td>NS</td>
</tr>
<tr>
<td>Daytime systolic BP (mm Hg)</td>
<td>144.2 (\pm) 12.3</td>
<td>146.5 (\pm) 13.7</td>
<td>NS</td>
</tr>
<tr>
<td>Daytime diastolic BP (mm Hg)</td>
<td>89.1 (\pm) 8.9</td>
<td>85.1 (\pm) 10.2</td>
<td>NS</td>
</tr>
<tr>
<td>Night-time systolic BP (mm Hg)</td>
<td>119.6 (\pm) 10.1</td>
<td>140.1 (\pm) 15.4</td>
<td>(&lt; .001)</td>
</tr>
<tr>
<td>Night-time diastolic BP (mm Hg)</td>
<td>73.32 (\pm) 9.0</td>
<td>83.9 (\pm) 12.4</td>
<td>(&lt; .005)</td>
</tr>
<tr>
<td>24-h heart rate (beats/min)</td>
<td>74.0 (\pm) 7.2</td>
<td>74.5 (\pm) 6.8</td>
<td>NS</td>
</tr>
<tr>
<td>Daytime heart rate (beats/min)</td>
<td>77.0 (\pm) 7.1</td>
<td>75.5 (\pm) 7.6</td>
<td>NS</td>
</tr>
<tr>
<td>Night-time heart rate (beats/min)</td>
<td>63.4 (\pm) 9.6</td>
<td>62.2 (\pm) 9.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

\(BP = \) blood pressure.

Mean values \(\pm\) SD.
LV mass (g) 160.9
LV mass/body surface area (g/m^2) 85.2
LV posterior wall thickness (mm) 8.8
Interventricular septum thickness (mm) 9.3
E-wave deceleration time (msec) 205.0
LV end-systolic diameter (mm) 25.8
E/A ratio 0.99
LV end-diastolic diameter (mm) 45.9
LV mass/height^2.7 (g/m^2.7) 39.9
LV mass (g) 160.9 ± 35.3
LV mass/body surface area (g/m^2) 85.2 ± 16.6
LV mass/height^2.7 (g/m^2.7) 39.9 ± 9.0
E/A ratio 0.99 ± 0.19
E-wave deceleration time (msec) 205.0 ± 31.6

Table 3. Echocardiographic features of the study groups

<table>
<thead>
<tr>
<th></th>
<th>Dippers</th>
<th>Nondippers</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrium diameter (mm)</td>
<td>30.9 ± 5.9</td>
<td>31.7 ± 6.3</td>
<td>NS</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>45.9 ± 3.3</td>
<td>47.2 ± 4.0</td>
<td>NS</td>
</tr>
<tr>
<td>LV end-systolic diameter (mm)</td>
<td>25.8 ± 3.1</td>
<td>25.2 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td>Interventricular septum thickness (mm)</td>
<td>9.3 ± 1.2</td>
<td>10.0 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>LV posterior wall thickness (mm)</td>
<td>8.8 ± 1.2</td>
<td>9.5 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.40 ± 0.06</td>
<td>0.42 ± 0.07</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>160.9 ± 35.3</td>
<td>178.7 ± 58.2</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass/body surface area (g/m^2)</td>
<td>85.2 ± 16.6</td>
<td>89.7 ± 22.7</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass/height^2.7 (g/m^2.7)</td>
<td>39.9 ± 9.0</td>
<td>42.0 ± 9.6</td>
<td>NS</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.99 ± 0.19</td>
<td>0.89 ± 0.24</td>
<td>NS</td>
</tr>
<tr>
<td>E-wave deceleration time (msec)</td>
<td>205.0 ± 31.6</td>
<td>223.6 ± 39.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

LV = left ventricular.
Mean values ± SD.

of HOMA index and adiponectin with systolic/diastolic BP levels, either clinic or 24-h ambulatory, was found.

**Echocardiographic Data**

The echocardiographic parameters of dipper and nondipper patients are reported in Table 3. Nondippers showed LV mass, RWT, and E/A ratio similar to those of dippers. Left ventricular hypertrophy, according to LV mass/height^2.7, was observed in 3 of 20 dippers, and in 2 of 20 nondippers; concentric remodelling was observed in 3 of 20 dippers and in 2 of 20 nondippers. Nine subjects in dippers (45%) and 11 subjects in nondippers (55%) had diastolic dysfunction. No correlation between any demographic, clinical, biochemical, or hormonal parameters and echocardiographic parameters was found in the entire population.

**Discussion**

Many previous studies have determined that essential hypertension is often associated with insulin resistance, but it is not well established whether particular subsets of hypertensive patients are more insulin resistant than others. In agreement with findings in a large population, patients are more insulin resistant than others, but it is not well established whether particular subsets of hypertensive patients.33 Our nondipper patients did not have greater end-organ damage and increased mortality than dippers.34 Our two groups of patients showed similar LV mass, geometry, and diastolic function. Although LV structural and functional parameters were within the normal limits in the large majority of patients, diastolic function was abnormal (E/A ratio <1) in a considerable number of subjects from both groups. This could have occurred as our patients had a mild-to-moderate degree and relatively short duration of hypertension, and because they were selected as not having other major cardiovascular risk factors, such as diabetes, hyperlipidemia, obesity, smoking habit, which are independent contributors to cardiac alteration in hypertension.35–38

As a limitation of the study, the small size of the two groups of patients could have introduced a type 2 error, decreasing the significance of the statistical difference between the variables examined.

No correlation between adiponectin and BP levels, either clinic or 24-h ambulatory, was found in our patients, suggesting that adiponectin does not exert a direct effect on vascular tone. Our findings were in agreement with some reports,9,12 and at variance with others,11 where only clinic BP was considered. Plasma insulin and HOMA index were higher, and adiponectin levels were lower in our nondipper compared to dipper patients. Raji et al.39 found that 11 of their 12 nondipper hypertensive patients, in addition to a slight hypotensive effect, exhibited restoration of a normal circadian BP pattern after treatment with rosiglitazone, an insulin sensitizer agent. In this regard, there is evidence that adiponectin expression is regulated by peroxisome proliferator-activated receptor γ-dependent pathways. Because adiponectin could be involved in the beneficial effects of thiazolidinediones on insulin sensitivity,40 therapeutic modulation of adiponectin might provide additional benefit to con-
ventional antihypertensive therapy in patients with a nondipper BP profile. The association of adiponectin, insulin resistance, and altered circadian pressure profile may determine the increase of the cardiovascular risk observed in nondipper hypertension. This should be demonstrated with long-term follow-up studies in patients with this clinical characteristic.

In summary, in the absence of major cardiovascular risk factors, nondipper essential hypertensive patients show more prominent insulin resistance and lower adiponectin levels compared to dippers. Therapeutic modulation of adiponectin or insulin resistance might provide additional benefit to conventional antihypertensive treatment.

Acknowledgments
We thank Marilena Tormene and Sonia Leonardi for skillful technical assistance, and Dr. Edoardo Casiglia for his support in revising statistical analysis.

References