Effects of Time of Day of Treatment on Ambulatory Blood Pressure Pattern of Patients With Resistant Hypertension

Ramón C. Hermida, Diana E. Ayala, Carlos Calvo, José E. López, Artemio Mojon, María J. Fontao, Rita Soler, José R. Fernández

Abstract—Patients with resistant hypertension present high prevalence of a non-dipper blood pressure pattern. Recent results indicate that non-dipping is related partly to the absence of 24-hour therapeutic coverage in patients treated with single morning doses. Accordingly, we investigated the impact of treatment time on the blood pressure pattern in 700 patients with resistant hypertension on the basis of clinic measurements who were studied by 48-hour ambulatory monitoring. Among them, 299 patients received all their medication on awakening, and 401 were taking 1 antihypertensive drug at bedtime. The percentage of patients with controlled ambulatory blood pressure was double in patients taking 1 drug at bedtime ($P=0.008$). Among the 578 patients with true resistant hypertension, subjects receiving 1 drug at bedtime showed a significant reduction in the 24-hour mean of systolic and diastolic blood pressure (3.1 and 1.6 mm Hg, respectively; $P<0.011$). This reduction was much more prominent during nighttime (5.1 and 3.0 mm Hg; $P<0.001$). Accordingly, the diurnal/nocturnal blood pressure ratio was significantly increased by 2.7 and the prevalence on non-dipping reduced (56.9 versus 81.9%; $P<0.001$) in patients taking 1 drug at bedtime. Compared with patients receiving all drugs on awakening, subjects with 1 drug at bedtime also showed significant reductions in the average values of glucose, cholesterol, fibrinogen, and urinary albumin excretion ($P<0.011$). In patients with resistant hypertension, pharmacological therapy should take into account when to treat with respect to the rest–activity cycle of each patient to improve control and to avoid the non-dipper pattern associated to higher cardiovascular risk. (Hypertension. 2005;46[part 2]:1053-1059.)

Key Words: blood pressure monitoring, ambulatory ■ circadian rhythm

Hypertension has been defined as resistant to treatment, or refractory, when a therapeutic plan that has included attention to lifestyle measures and the prescription of ≥3 antihypertensive drugs in adequate doses has failed to lower systolic blood pressure (SBP) and diastolic blood pressure (DBP) sufficiently. Patients with resistant hypertension are at a greater risk for stroke, renal insufficiency, and morbidity cardiovascular events than patients whose blood pressure (BP) is well controlled by medical therapy. Indeed, in patients with resistant hypertension, poor BP control may engender a consistent amount of target organ damage, and this, in turn, may become a cause of resistance to treatment.

It has also been reported that most patients receiving antihypertensive therapy show a “white-coat effect” that could cause an overestimation of their real BP. The impact of this effect on the occurrence of resistant hypertension seems to be highly variable among different studies, ranging from 20% up to 43% of the patients. Ambulatory BP monitoring (ABPM) is the only method to differentiate “isolated office resistant hypertension” from “true resistant hypertension.” It has thus been suggested that ABPM should be performed as an initial evaluation of all patients with potential resistant hypertension. ABPM has the added advantage to provide higher prognostic value than office BP measurements in the evaluation of patients with resistant hypertension. With the use of ABPM, Muxfeldt et al reported a 69% prevalence of non-dipping (<10% decline in nocturnal mean relative to the diurnal mean of BP) in patients with true resistant hypertension, a prevalence ≈20% higher than that found in patients with isolated office resistant hypertension in the same study. No attention was paid in this trial to the time of day of antihypertensive treatment. However, recent results indicate that non-dipping is partly related to the absence of homogeneous 24-hour therapeutic coverage in patients treated with single morning doses. Accordingly, we investigated the impact of treatment time on the circadian BP pattern, on the degree of BP control, and on potential differences in relevant analytical parameters in patients with true resistant hypertension who were evaluated by 48-hour ABPM for improved reproducibility in their dipper classification.

Received April 27, 2005; first decision May 19, 2005; revision accepted May 25, 2005.

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Hypertension is available at http://www.hypertensionaha.org DOI: 10.1161/01.HYP.0000172757.96281.bf

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Methods

Subjects
The study was conducted at the Hypertension and Vascular Risk Unit, Hospital Clínico Universitario, Santiago de Compostela, Spain, between January 2002 and November 2004. Shift workers, heavy drinkers (alcohol intake >80 g per day), and heavy smokers (>20 cigarettes per day), and heavy exercisers were excluded, as were individuals with secondary arterial hypertension (including obstructive sleep apnea) and cardiovascular disorders, including angina, heart failure, stroke, nephropathy, and retinopathy or previous myocardial infarction or coronary revascularization, as revealed by thorough clinical evaluation according to the standardized protocol at the unit. Inclusion criteria required a diagnosis of uncontrolled hypertension on the basis of conventional BP measurements (SBP ≤140 mm Hg or DBP ≥90 mm Hg) in patients treated for ≥3 months with a stable scheme consisting of ≥3 antihypertensive drugs, with an adequate combination and dose. 1 With these inclusion criteria, we identified 721 patients, and 700 completed the study and provided all required information (see below). Among these, 299 subjects were receiving all their medication on awakening, and 401 were taking ≥1 antihypertensive drug at bedtime, as prescribed randomly by their respective physicians. A total of 578 participants (295 men and 283 women) 59.2±11.3 years of age showed uncontrolled ABPM and were thus considered patients with true resistant hypertension. Uncontrolled hypertension based on ABPM in this study required that either the 24-hour mean SBP/DBP be >130/80 mm Hg, the diurnal mean be >135/85 mm Hg, or the nocturnal mean be >120/70 mm Hg. 12,13 The demographic characteristics of the patients with true resistant hypertension are described in Table 1. Blood samples were obtained in the clinic from the antecubital vein after nocturnal fasting between 8 AM and 9 AM on the same days when 48-hour ABPM was initiated. Patients collected their urine during the first 24 hours of ABPM. Blood and urine were analyzed for the variables described in Table 1 using routine automatic techniques at the hospital laboratory. Clinic BP measurements (6 per visit after being seated for 5 minutes, on the same day just before starting ABPM) were obtained between 9 AM and 10 AM, before the patients took their morning medication. These measurements were always obtained by the same investigator with a validated automated oscillometric device (HEM-737; Omron Health Care Inc.), 14 The state ethics committee of clinical research approved the study.

ABPM Assessment
After providing signed informed consent to participate in this study, the SBP, DBP, and heart rate (HR) of each participant were automatically measured every 20 minutes from 7 AM to 11 PM and every 30 minutes during the night for 48 consecutive hours with a properly calibrated SpaceLabs 90207 device (SpaceLabs Inc.). Participants were instructed to go about their usual activities with minimal restrictions but to follow a similar schedule during the 2 days of ABPM and to avoid daytime napping. No one was hospitalized during monitoring. ABPM always began between 10 AM and 12 PM. BP series were not considered valid for analysis if >30% of the measurements were lacking, if data were missing for >2-hour spans, if data were collected from subjects while experiencing an irregular rest–activity schedule, or if the nighttime sleep span was <6 hours or >12 hours during monitoring. Protocol-correct data series were collected from 700 subjects. ABPM profiles of 21 additional subjects were eliminated because they were invalid following those criteria set a priori.

Actigraphy
During the continuous 48-hour ABPM, each participant wore a Mini-Motion-Logger actigraph (Ambulatory Monitoring Inc.) on the dominant wrist to monitor the level of physical activity at 1-minute intervals. This compact (about half the size of a wrist watch) device functions as an accelerometer. The internal clocks of the actigraph and the ABPM devices were synchronized through their respective interfaces by the same computer. The actigraphy data were used to determine the onset and offset times of diurnal activity and nocturnal sleep to make possible the accurate calculation of the diurnal and nocturnal BP means of each subject. The mean activity for the 5 minutes before each BP reading was then calculated for further statistical analysis on circadian variability of activity according to previous studies on this area. 10,15

Statistical Methods
For group analysis, each individual’s clock hour BP and HR values were first referenced to hours after awakening from nocturnal sleep using the information obtained from wrist actigraphy. This transfor-
mation avoided the introduction of bias attributable to differences among subjects in their sleep/activity routine. BP and HR time series were edited according to conventional criteria to remove measurement errors and outliers. Thus, readings with SBP >250 or <70 mm Hg, DBP >150 or <40 mm Hg, and pulse pressure (PP; difference between SBP and DBP) >150 or <20 mm Hg were discarded automatically.

For descriptive and comparative purposes, the circadian rhythm of BP, HR, and wrist activity was assessed for each group of patients divided according to their treatment schedule (either all antihypertensive drugs on awakening or not) by population multiple-component analysis, a method applicable to nonsinusoidal shaped hybrid time series data (time series collected from a group of subjects) consisting of values distributed at equal or unequal intervals. The circadian rhythm parameters of midline estimating statistic of rhythm (average value of the rhythmic function fitted to the data), overall amplitude (one half the difference between the maximum and the minimum values of the best-fitted curve), and orthophase (peak time, expressed as a lag from the time of awakening from nocturnal sleep) were compared between groups with a nonparametric test developed to assess differences in parameters derived from population multiple-components analysis. Hourly BP means were compared between both groups of patients by ANOVA (quantitative variables) or testing with the Holm procedure. The daily (24-hour), diurnal, and nocturnal means of BP were further compared among groups by multiple-components analysis. Arrows descending from upper horizontal axis point to the circadian orthophase (rhythm crest time).

### Results

**Ambulatory BP Control**

Among the 700 patients who completed the study, 122 (17.4%) had controlled BP according to all ABPM criteria mentioned above. The percentage of controlled patients was significantly higher (20.7%) among patients taking 1 antihypertensive drug at bedtime compared with patients treated with all drugs on a single morning dose (13.0%; \( P=0.008 \)). An angiotensin II receptor blocker (ARB) or an angiotensin-converting enzyme inhibitor (ACEI), in combination with a diuretic, were included in the treatment scheme of 96.2% of the controlled patients.

**Demographic Characteristics and Analytical Parameters (true resistant hypertension)**

The 2 groups of patients with true resistant hypertension (uncontrolled ABPM) divided as a function of their treatment regimen were comparable in terms of the number and class of antihypertensive drugs used for treatment (Table 1). The most frequent combinations were ARB (63%) or ACEI (31%) with a diuretic, and a calcium channel blocker (66%) or an \( \alpha \)-blocker (27%) as the third drug. \( \beta \)-Blockers were used by 25% of the patients in both groups. The comparison of cardiovascular risk factors indicates the lack of differences among groups in the prevalence of type 2 diabetes, dyslipidemia, current smoking (\( \leq 20 \) cigarettes per day), obesity (body mass index [BMI] \( \geq 30 \) kg/m\(^2\)), and sedentary lifestyle (no regular physical activity of \( \geq 30 \) minutes per day for \( \geq 2 \) days per week), as determined by questionnaire and personal interview with each patient.

The 2 groups of subjects were also comparable in age, BMI, and waist and hip perimeters (Table 1). Clinic BP measurements, including PP, were slightly but significantly reduced in patients receiving bedtime treatment. Results also indicate a significant reduction in the average values of glucose, cholesterol, fibrinogen and 24-hour urinary albumin excretion in patients with true resistant hypertension treated with 1 drug at bedtime (Table 1). The reduction in total cholesterol was mainly attributable to the significant reduction in LDL cholesterol. The percentage of patients with proteinuria (albumin >300 mg per 24 hours) was slightly higher in patients receiving all drugs on awakening (14.3 versus 10.1%). Differences among groups in albumin excretion were significant even after exclusion of patients with proteinuria (Table 1).

**ABPM Characteristics (true resistant hypertension)**

The circadian rhythm of SBP (left) and DBP (right) of both groups of patients with true resistant hypertension divided according to the time of day of treatment is depicted in Figure 1. Results indicate a marked reduction in BP during the middle of diurnal active hours, higher than the described postprandial valley in either normotensive subjects or untreated hypertensive patients. Because of the absence of diurnal napping corroborated by wrist actigraphy, this diurnal reduction in BP seems to be related, as reported previously, to the effects of single morning dosing with antihypertensive drugs of low smoothness index, such as most ACEI,
TABLE 2. Ambulatory BP Characteristics of Patients With True Resistant Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Drugs on Awakening</th>
<th>One Drug at Bedtime</th>
<th>P for Group Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>260</td>
<td>318</td>
<td>0.550</td>
</tr>
<tr>
<td>Duration of nocturnal rest, hours</td>
<td>8.9±1.2</td>
<td>8.9±1.2</td>
<td>0.550</td>
</tr>
<tr>
<td>Diurnal mean of SBP, mm Hg</td>
<td>139.3±15.3</td>
<td>137.3±14.5</td>
<td>0.049</td>
</tr>
<tr>
<td>Nocturnal mean of SBP, mm Hg</td>
<td>133.5±18.2</td>
<td>128.4±16.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-hour mean of SBP, mm Hg</td>
<td>137.5±15.1</td>
<td>134.4±14.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Diurnal/nocturnal ratio of SBP, %</td>
<td>4.1±8.8</td>
<td>6.3±8.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diurnal mean of DBP, mm Hg</td>
<td>82.8±11.0</td>
<td>82.0±10.7</td>
<td>0.205</td>
</tr>
<tr>
<td>Nocturnal mean of DBP, mm Hg</td>
<td>74.9±10.7</td>
<td>71.9±10.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-hour mean of DBP, mm Hg</td>
<td>80.3±10.4</td>
<td>78.7±9.9</td>
<td>0.011</td>
</tr>
<tr>
<td>Diurnal/nocturnal ratio of DBP, %</td>
<td>9.2±8.6</td>
<td>11.9±9.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*All values given in mean±SD.

Diurnal/nocturnal ratio, an index of BP dipping, is defined as percent decline in BP during hours of nocturnal rest relative to the mean BP obtained during the hours of diurnal activity.

ο-blockers, and β-blockers. The BP reduction starting shortly after awakening (in this study, corresponding to the treatment time of morning dosing) is almost comparable to the nocturnal decline in SBP, mainly for patients receiving all drugs on awakening. Accordingly, a high 81.9% of the patients in this group presented a non-dipper BP pattern (here, defined as patients with <10% in diurnal/nocturnal BP ratio, calculated as the percent decline in nocturnal mean compared with the diurnal mean of BP, using all data sampled by ABPM for 48 consecutive hours).

Compared with patients receiving all drugs on awakening, patients with true resistant hypertension who were receiving 1 antihypertensive drug at bedtime show a significant reduction in the 24-hour mean of SBP and DBP. Differences in hourly averages of BP among groups were statistically significant at all nighttime hours. The circadian amplitude (extent of change in BP along the 24 hours) was also significantly higher in patients receiving 1 drug at bedtime (Figure 1) as a consequence of a greater effect of timed therapy on the nocturnal compared with the diurnal mean of BP. Conclusions on the circadian variability of BP are unchanged if results are based on all available patients, including those with controlled ABPM. Because of the greater percentage of controlled patients among those receiving 1 drug at bedtime, differences in BP among groups, shown in Figure 1 for patients with true resistant hypertension, are even higher when results are based on data from all participants in this study. Despite differences in BP among groups shown in Figure 1, there is no significant difference in HR as a function of time of treatment (difference of 0.15 bpm; P=0.870). The circadian pattern of physical activity was also similar between groups (24-hour mean of 121 and 122 counts per min for patients receiving all drugs on awakening or 1 drug at bedtime, respectively; P=0.731). Average duration of nocturnal rest was not statistically different among groups (P=0.550; Table 2).

Figure 2 provides additional information on the comparison between the groups in the diurnal, nocturnal, and 24-hour mean BP values. Results from ANOVA indicate the significant BP reduction, mainly in nocturnal mean, when patients received 1 drug at bedtime (Table 2). The effect of timed treatment was significantly greater in the nocturnal compared with the diurnal mean of BP. Accordingly, the diurnal/nocturnal BP ratio (an index of BP dipping) was significantly increased when 1 drug was administered at bedtime compared with the average ratio of patients receiving 1 drug on awakening (Table 2). The prevalence of non-dipping was significantly reduced to 56.9% in patients receiving 1 drug at bedtime (P<0.001; Table 1).

Discussion

Therapeutic strategies in resistant hypertension currently include adding another drug or changing 1 drug for a different drug in search of a potentially better synergic combination. It has been reported previously that up to 89% of treated hypertensive patients, including those with resistant hypertension, receive all their antihypertensive drugs in a single morning dose. Results from efficacy studies of antihypertensive medications have been reported mainly without paying attention to the time of day of drug administration. However, appreciable ingestion time differences in the kinetics of BP lowering and cardiac medications are well known. They result from circadian rhythms in gastric pH and emptying, gastrointestinal motility, biliary function and circulation, liver enzyme activity, and blood flow to the duodenum, kidney and other organs, among other factors. Clinically relevant dosing time differences in the beneficial and adverse
effects of BP-lowering medications are also known. They result from the chronokinetics of the medications as well as circadian rhythms in drug-free fraction, rate-limiting steps of key metabolic pathways, receptor number and conformation, or second messenger dynamics. Differences in efficacy or adverse effects depending on the circadian time of drug administration have been clearly identified, among other BP-lowering drugs, for nifedipine, nitrendipine, isradipine, benazepril, captopril, enalapril, perindopril, quinapril, ramipril, trandolapril, doxazosin, torasemide, and valsartan. Such chronotherapeutic differences in effects also apply to combination therapy, as demonstrated previously when amlodipine, captopril, or doxazosin were used in combination with other antihypertensive drugs. However, the potential impact of the time of day of antihypertensive treatment in patients with resistant hypertension has not been investigated previously.

Results from this cross-sectional study in patients with resistant hypertension first indicate that chronotherapy markedly increases BP control. The percentage of patients with diurnal, nocturnal, and 24-hour mean BP values below currently accepted diagnostic thresholds of hypertension in this study is almost double within those patients receiving 1 drug at bedtime compared with patients with a treatment strategy consisting of administering all drugs on awakening. A previous study on a small number of patients with resistant hypertension has also suggested that a combination of ABPM with chronotherapy, by administering drugs at times of the day synchronized with peaks of BP, was recommended for increasing BP control. Moreover, in an independent prospective trial, we randomized patients with resistant hypertension who were receiving 3 drugs on a single morning dose to 1 of 2 groups according to the modification in their treatment strategy: changing 1 of the drugs, but keeping all 3 in the morning, or the same approach but administering the new drug at bedtime. The percentage of patients with controlled ambulatory BP after intervention increased from 3% to 35% when patients were scheduled to receive 1 drug at bedtime.

Results from Table 1 indicate a high prevalence of an altered non-dipper BP profile in patients with true resistant hypertension receiving all drugs on awakening. A high prevalence of non-dipping was noted previously in another study on the 24-hour pattern of ABPM in resistant hypertension. In this previous study, patients with true resistant hypertension showed even higher nocturnal mean of BP and higher prevalence of non-dipping than patients with isolated office-resistant hypertension. However, no attention was paid in this trial to the time of antihypertensive treatment. The authors reported a 68.9% prevalence of non-dipping, almost identical to the 68.2% prevalence found in our study when all patients were evaluated as a single group without taking into account their treatment schedule (Table 1). Figures 1 and 2 indicate a marked reduction in ambulatory BP, mainly during the hours of nocturnal rest, when patients with resistant hypertension were treated with 1 drug at bedtime. The greater effect of this chronotherapeutic approach on the nocturnal compared with the diurnal mean of BP resulted in a significant reduction in the prevalence of non-dipping from 81.9% to 56.9% when patients received 1 drug at bedtime (Table 1). This result may be particularly relevant because 2 independent prospective studies have concluded that nighttime BP is a better predictor of cardiovascular mortality than the diurnal or the 24-hour means of BP.

Non-dipper hypertension, which is characterized by the loss or even reversal of the expected 10% to 20% sleep time BP decline, is associated with elevated risk of end-organ injury, particularly to the heart (left ventricular hypertrophy and myocardial infarct), brain (stroke), and kidney (albuminuria and progression to end-stage renal failure). Non-dipper BP patterning is more frequent in hypertension that is secondary to specific medical conditions, such as chronic renal failure, diabetes, and autonomic nervous system dysfunction than in uncomplicated primary hypertension. However, results from a recent study indicate a high 38% prevalence of non-dipping among untreated patients with essential hypertension. Most important, the percentage of non-dipper patients significantly increases to 62% when patients are evaluated by 48-hour ABPM under the effect of antihypertensive therapy. The percentage of patients who were receiving all their antihypertensive drugs in a single morning dose was significantly higher among non-dipper (91%) compared with dipper patients (59%), thus suggesting that non-dipping among treated patients is partly attributable to the lack of 24-hour therapeutic coverage of many antihypertensive drugs used in single morning dosing. Results from Table 1 and Figure 1 lead to this same conclusion, mainly taking into account the lack of differences among the groups being compared in either the number or the class of antihypertensive drugs used in their therapeutic scheme.

The BP pattern in patients with resistant hypertension shows a 12-hour component more prominent than the usually more significant 24-hour component that characterizes most subjects with either normotension or untreated hypertension. Accordingly, BP presents a bimodal waveform with 2 prominent peaks, 1 shortly after awakening and a second in the evening (~12 hours after awakening; Figure 2). In the absence of changes in the circadian pattern of physical activity, this BP pattern in resistant hypertension seems to be attributable to the effects of short-acting antihypertensive medication. Lack of proper BP control in the late afternoon may be a causal factor of a secondary peak of cardiac and cerebrovascular incidents seen at that time of the day. Community-based studies reveal an almost identical 24-hour variation in the clock time of angina pectoris, myocardial infarction, sudden cardiac death, ischemic and hemorrhagic stroke, and transient ischemic attacks. In all cases, different studies have confirmed a prominent morning peak and a smaller second peak later in the day. The potential relation of this evening peak in events to the altered BP waveform seen, as an example, in patients with resistant hypertension, deserves further investigation.

Normalization of the circadian BP rhythm is considered to be an important clinical goal of pharmacotherapy because it may slow the advance of renal injury and avert end-stage renal failure. In this study, patients receiving 1 drug at bedtime, apart from an increased BP control and a more dipper BP pattern, also show a significant decrease in urinary
albumin excretion (Table 1). Differences in albumin among groups are significant even after excluding from analysis the patients with proteinuria (more prevalent among subjects treated with all drugs on awakening), having extremely large albumin values that markedly distort group comparisons. There is growing evidence that reduction of urinary albumin excretion provides renal protection and reduces cardiovascular risk. 

Patients treated with 1 drug at bedtime are also characterized by a decrease in plasma glucose. This result seems even more relevant taking into account that the prevalence of previously diagnosed type 2 diabetes was exactly the same in both groups (Table 1). Moreover, with a similar prevalence of dyslipidemia in both groups of patients, total cholesterol and LDL cholesterol were significantly lower in patients receiving 1 drug at bedtime. Finally, plasma fibrinogen was also significantly lower in this group of patients with true resistant hypertension (Table 1). Clinical trials and epidemiological observations have indicated that elevated plasma fibrinogen levels are strongly correlated with an increased frequency of vascular events, thus recognizing fibrinogen as a significant parameter for assessing the potential risk of acute myocardial infarction and stroke. Previous results have already established that plasma fibrinogen is significantly elevated in non-dipper compared with dipper hypertensives. The potential reduction in fibrinogen, among other cardiovascular risk factors, associated to the normalization of the BP profile from a non-dipper to a dipper pattern needs to be investigated prospectively.

**Perspectives**

Results from this study on patients with true resistant hypertension indicate that time of treatment in relation to the rest–activity cycle of each individual subject represents a key factor for the proper modeling of the circadian BP pattern. This chronotherapeutic approach results in a significant 60% increase in the prevalence of patients with controlled BP after treatment, a significant 32% decrease in the prevalence of patients with a non-dipper BP pattern, and statistically significant reductions in the mean values of relevant markers of end-organ damage and cardiovascular mortality, namely plasma glucose, total cholesterol, LDL cholesterol, plasma fibrinogen, and urinary albumin excretion. In patients with resistant hypertension, pharmacological therapy should take into account when to treat with respect to the rest–activity cycle of each patient, to improve control and to avoid the non-dipper pattern associated to higher cardiovascular risk.

**Acknowledgments**

This research was supported in part by grants from Xunta de Galicia (PGIDIT03-PXIB-32201PR), and Vicerrectorado de Investigación, University of Vigo.

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Hypertension. 2005;46:1053-1059; originally published online August 8, 2005; doi: 10.1161/01.HYP.0000172757.96281 bf

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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