Is Isolated Nocturnal Hypertension a Novel Clinical Entity?: Findings From a Chinese Population Study

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Is Isolated Nocturnal Hypertension a Novel Clinical Entity?  
Findings From a Chinese Population Study

Yan Li, Jan A. Staessen, Lu Lu, Li-Hua Li, Gu-Liang Wang, Ji-Guang Wang

Abstract—We reported previously that normotensive Chinese had higher nighttime diastolic blood pressure compared with non-Chinese. We, therefore, studied the prevalence and characteristics of isolated nocturnal hypertension (HT) and its association with arterial stiffness, an intermediate sign of target organ damage. We recorded ambulatory blood pressure, the central and peripheral systolic augmentation indexes, the ambulatory arterial stiffness index, and brachial-ankle pulse wave velocity in 677 Chinese enrolled in the JingNing population study (53.6% women; mean age: 47.6 years). Prevalence was 10.9% for isolated nocturnal HT (≥120/70 mm Hg from 10:00 PM to 4:00 AM), 4.9% for isolated daytime HT (≥135/85 mm Hg from 8:00 AM to 6:00 PM), and 38.4% for day-night HT. Patients with isolated nocturnal HT, compared with subjects with ambulatory normotension (45.8%), were older (53.7 versus 40.7 years), more often referred patients, each 10-mm Hg increment in the nighttime diastolic blood pressure that was, on average, 3 to 12 mm Hg higher. Based on these observations,9,11,12 we envisaged that some subjects might have an elevated nighttime blood pressure in the presence of a normal daytime level, a condition that we termed isolated nocturnal hypertension. We further hypothesized that this special type of hypertension, which can only be diagnosed by 24-hour ambulatory monitoring, might be associated with target organ damage. To test our hypothesis, we studied the prevalence and characteristics of isolated nocturnal hypertension in a Chinese population and examined its association with various indexes of arterial stiffness.

Key Words: ambulatory blood pressure monitoring ■ arterial stiffness ■ blood pressure ■ pulse wave velocity ■ systolic augmentation

Already in 1988, O'Brien et al1 reported that an abnormal circadian blood pressure profile with decreased nighttime dipping led to a higher risk of cerebrovascular complications. Subsequent studies of populations2–4 and hypertensive cohorts5–8 corroborated that an elevated nocturnal blood pressure is a harbinger of an unfavorable outcome. In Ohasama residents, each 5% decrease in the nocturnal blood pressure fall was associated with an ≈20% greater risk of cardiovascular mortality.3 Similarly, in an Irish cohort of referred patients, each 10-mm Hg increment in the nighttime systolic pressure resulted in a 21% higher cardiovascular mortality, whereas the corresponding estimate for a 5-mm Hg diastolic increment amounted to 9%.8 Several studies suggested that Asians3,9 and blacks10,11 have less nocturnal blood pressure dipping than whites. Along these lines, we noticed previously that, among the normotensive subjects enrolled in 7 population studies, Chinese compared with non-Chinese consistently had a nighttime diastolic blood pressure that was, on average, 3 to 12 mm Hg higher.12 Based on these observations,9,11,12 we envisaged that some subjects might have an elevated nighttime blood pressure in the presence of a normal daytime level, a condition that we termed isolated nocturnal hypertension. We further hypothesized that this special type of hypertension, which can only be diagnosed by 24-hour ambulatory monitoring, might be associated with target organ damage. To test our hypothesis, we studied the prevalence and characteristics of isolated nocturnal hypertension in a Chinese population and examined its association with various indexes of arterial stiffness.

Methods

Study Population

In the framework of our ongoing Chinese study on genes involved in hypertension,13,14 from 2003 through 2005, we recruited participants from 14 villages in the JingNing County, a rural area ∼500 km south of Shanghai. The ethics committee of Ruijin Hospital and Shanghai Jiaotong University Medical School approved the study. We invited all of the villagers with a minimum age of 12 years to take part. Of

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2059 eligible subjects, 1490 gave informed written consent. The participation rate was 72.4%.

At the time of writing of this report, 733 participants had their ambulatory blood pressure measured. We excluded 31 participants from analysis because their ambulatory recordings had durations of <20 hours (n=1), included <10 daytime (n=2) or 5 nighttime (n=14) readings, or because the subjects had no measurements of their arterial properties (n=14).

**Ambulatory Blood Pressure Monitoring**

In keeping with the methods used in other population studies, we programmed oscillometric SpaceLabs 90207 monitors (SpaceLabs Inc)• to obtain blood pressure readings at 20-minute intervals from 8 AM until 10 PM and every 45 minutes from 10 PM to 8 AM. We checked the calibration of these devices each month against a mercury column. If the ambulatory recordings were Isolated nocturnal or daytime hypertension, respectively. Thus, the whether, in untreated conditions, these 25 patients would have pressures in the day-night hypertensive group. We excluded 25 patients who, on antihypertensive drug treatment, had either a normal conditions were present or absent, we classified subjects as having combined day-night hypertension or as normotensive on ambulatory measurement. Of 96 patients on antihypertensive drug treatment, we included 71 with elevation of both their daytime and nighttime blood pressures in the day-night hypertensive group. We excluded 25 patients who, on antihypertensive drug treatment, had either a normal daytime or normal nighttime blood pressure. We could not ascertain whether, in untreated conditions, these 25 patients would have isolated nocturnal or daytime hypertension, respectively. Thus, the number of participants included in the present analysis totaled 677.

**Measurement of Arterial Properties**

We measured the arterial characteristics under standardized conditions in a quiet examination room, after the subjects had rested for 10 minutes in the supine position. Participants refrained from smoking, heavy exercise, and drinking alcohol for ≥2 hours before the examination.

In all of the participants (n=677), a single observer recorded the radial arterial waveform at the dominant arm using a high-fidelity SPC-301 micromanometer (Millar Instruments, Inc) interfaced with a laptop computer running the SphygmoCor software, version 7.1 (AtCor Medical Pty Ltd). The radial and central augmentation indexes were the ratios of the second to the first shoulder of the systolic upstroke. From unedited 24-hour recordings, we defined the ambulatory arterial stiffness index as 1 minus the regression slope of diastolic on systolic blood pressure. In 333 unselected subjects, we also measured brachial-ankle pulse wave velocity using an automated waveform analyzer (Colin VP-1000, Colin Medical Technology). For analysis, we used the average of left and right pulse wave velocities. The intraobserver coefficient of variation was 8.7% for the brachial-ankle pulse wave velocity and 6.7% and 9.2% for the peripheral and central augmentation indexes, respectively.

**Other Clinical and Biochemical Measurements**

At a local examination center in each village, one physician (G.-L.W.) measured conventional blood pressure using a standard mercury sphygmomanometer according to the 2005 European guidelines. Five consecutive blood pressure readings in each participant were averaged for analysis. Office hypertension was a blood pressure at the examination center of ≥140 mm Hg systolic or 90 mm Hg diastolic or the use of antihypertensive drugs. During the home visit, the observers administered a standardized questionnaire to collect information on smoking habits, alcohol intake, physical activity, and the use of medications. Published tables allowed us to compute the energy spent in physical activity from body weight and from the duration and type of physical activity during work and leisure time. Venous blood samples, collected after overnight fasting, were analyzed for blood glucose and the serum concentration of lipids by automated enzymatic methods. Within 2 to 3 weeks of the home visit, the participants collected a 24-hour urine sample in a wide-neck plastic container for measurement of sodium and creatinine excretion.

**Comparison With the International Database**

To evaluate the consistency of our current findings in an international context, we investigated the prevalence of isolated daytime and isolated nocturnal hypertension in the International Database of Ambulatory Blood Pressure Monitoring. We only considered subjects not on antihypertensive drug treatment, enrolled in population-based surveys in Western Europe (Belgium, Italy, and Ireland), Eastern Europe (Bulgaria, Poland, Romania, and the Russian Federation), South Africa, and Japan. Statistical Analysis

For database management and statistical analyses, we used SAS software, version 9.1 (SAS Institute Inc). We compared means and proportions by a large sample z test and Fisher’s exact test, respectively. Using a stepwise multiple regression procedure with the P value for independent variables to enter and stay in the model set at 0.10, we identified sex, age, body height, and pulse rate as covariates of the arterial stiffness indexes. We performed multivariate-adjusted comparisons between groups, using a generalized linear model providing P values for overall and pairwise differences. To search for a set of variables possibly detecting patients with isolated nocturnal hypertension in the presence of normotension on conventional blood pressure measurement, we used a stepwise discriminant procedure.

**Results**

**Prevalence of Subtypes of Ambulatory Hypertension**

Among the 677 participants, 310 (45.8%) were normotensive on both daytime and nighttime blood pressure measurements, 33 (4.9%) had isolated daytime hypertension, 74 (10.9%) had isolated nocturnal hypertension, and 260 (38.4%) had day-night hypertension. Figure 1 illustrates the circadian blood pressure profiles of these 4 groups.

**Characteristics of the Subjects by Subtypes of Ambulatory Hypertension**

Table 1 lists the characteristics of the participants according to the 4 subgroups by ambulatory blood pressure status. Compared with subjects with ambulatory normotension, patients with isolated daytime hypertension were more obese and had a faster pulse rate during the day and night. Patients with isolated nocturnal hypertension were older, had a faster pulse rate at night, had higher serum concentration of total and high-density lipoprotein cholesterol, and had higher blood glucose. They also more frequently reported alcohol intake. Of the 74 patients with isolated nocturnal hypertension, only 4 (5.4%) also had hypertension on conventional blood pressure measurement. We searched for a set of characteristics possibly identifying the 70 patients with isolated nocturnal hypertension among the 531 subjects with normotension on conventional blood pressure measurement. In a stepwise discriminant procedure, we
considered the variables listed in Table 1. Only age ($P<0.001$) and current alcohol intake ($P=0.05$) entered the model. However, the resulting linear discriminant function failed to correctly identify any patient with isolated nocturnal hypertension.

### Arterial Stiffness Indexes by Subtypes of Ambulatory Hypertension

In continuous analyses of the whole study population, all of the examined indexes of arterial stiffness, both before and after adjustment for sex, age, body height, and pulse rate, were strongly and

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**TABLE 1. Characteristics of the Participants by Ambulatory Blood Pressure Status**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normotension (n=310)</th>
<th>Isolated Daytime Hypertension (n=33)</th>
<th>Isolated Nocturnal Hypertension (n=74)</th>
<th>Day-Night Hypertension (n=260)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n (%)</td>
<td>181 (58.4)</td>
<td>16 (48.5)</td>
<td>34 (46.0)</td>
<td>132 (50.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>Age, y</td>
<td>40.7±13.1</td>
<td>41.8±11.7</td>
<td>53.7±14.9§</td>
<td>54.8±13.7§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>21.9±2.6</td>
<td>23.3±3.4†</td>
<td>22.2±2.7</td>
<td>23.1±3.4§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daytime pulse rate, bpm</td>
<td>79.6±10.5</td>
<td>83.8±11.2†</td>
<td>79.6±10.7</td>
<td>79.4±11.2</td>
<td>0.18</td>
</tr>
<tr>
<td>Nighttime pulse rate, bpm</td>
<td>60.7±7.7</td>
<td>65.3±9.0‡</td>
<td>62.8±10.2†</td>
<td>61.7±8.2</td>
<td>0.007</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.77±0.94</td>
<td>4.84±0.97</td>
<td>5.12±0.97‡</td>
<td>5.14±1.05§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.50±0.33</td>
<td>1.41±0.27</td>
<td>1.63±0.46‡</td>
<td>1.57±0.44‡</td>
<td>0.004</td>
</tr>
<tr>
<td>Blood glucose, mmol/L</td>
<td>4.38±0.68</td>
<td>4.46±1.06</td>
<td>4.84±1.12‡</td>
<td>4.58±1.07†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary sodium excretion, mmol/d</td>
<td>173.8±79.3</td>
<td>184.9±86.1</td>
<td>150.1±75.3†</td>
<td>161.1±78.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Urinary sodium creatinine ratio</td>
<td>22.5±10.2</td>
<td>21.9±7.8</td>
<td>22.6±13.9</td>
<td>22.6±10.7</td>
<td>0.99</td>
</tr>
<tr>
<td>Physical activity, Kcal/d</td>
<td>3178±1251</td>
<td>3339±1381</td>
<td>3472±1429</td>
<td>3282±1698</td>
<td>0.45</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>83 (26.8)</td>
<td>10 (30.3)</td>
<td>27 (36.5)</td>
<td>82 (31.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Current drinking, n (%)</td>
<td>158 (51.0)</td>
<td>19 (57.6)</td>
<td>51 (68.9)§</td>
<td>148 (56.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Office hypertension, n (%)</td>
<td>6 (1.9)</td>
<td>5 (15.2‡)</td>
<td>4 (5.4)</td>
<td>131 (50.4§)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean±SD or number of subjects (%). HDL indicates high-density lipoprotein. $P$ values are for the overall differences among the 4 groups.

*Office hypertension was a conventional blood pressure of $\geq 140$ mm Hg systolic or $90$ mm Hg diastolic or use of antihypertensive drugs.

Significance of the difference with the normotensive reference group: †$P<0.05$; ‡$P<0.01$; §$P<0.0001$.
positively \((P<0.01)\) associated with the ambulatory blood pressure levels (Table 2). Figure 2 illustrates these associations across quartiles of the distributions of the daytime and nighttime systolic blood pressures. In multivariate-adjusted models, which included the daytime, as well as the nighttime, blood pressure, both blood pressure measurements remained significantly associated with the arterial indexes, with the exception of systolic nighttime blood pressure in relation to the central augmentation index (Table 2).

In categorical analyses, with adjustments applied for sex, age, body height, and pulse rate, patients with isolated daytime hypertension had higher central and peripheral systolic augmentation indexes and increased brachial-ankle pulse wave velocity than the normotensive reference group (Table 3). With similar adjustments applied, patients with isolated nocturnal hypertension and those with day-night hypertension, compared with group with ambulatory normotension, showed significant increases \((P<0.05)\) in all 4 of the measured indexes of arterial stiffness (Table 3).

**Sensitivity Analyses**

The groups with isolated daytime or nocturnal hypertension did not include any patient taking antihypertensive medications. In the day-night hypertensive group, the indexes of arterial stiffness remained significantly higher \((P<0.001)\) after exclusion of 71 patients on antihypertensive drug

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**TABLE 2. Relation Between Arterial Stiffness Indexes and Ambulatory Blood Pressures**

<table>
<thead>
<tr>
<th>Arterial Stiffness Indexes</th>
<th>Daytime Blood Pressure</th>
<th>Nighttime Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic (+10 mm Hg)</td>
<td>Diastolic (+5 mm Hg)</td>
</tr>
<tr>
<td></td>
<td>(+10 mm Hg)</td>
<td>(+5 mm Hg)</td>
</tr>
<tr>
<td>Central augmentation index, % (n=677)</td>
<td>6.01±0.55</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>3.26±0.48</td>
<td></td>
</tr>
<tr>
<td>Adjusted*</td>
<td>2.56±0.79§</td>
<td></td>
</tr>
<tr>
<td>Fully adjusted†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral augmentation index, % (n=677)</td>
<td>5.22±0.45</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.99±0.38</td>
<td></td>
</tr>
<tr>
<td>Adjusted*</td>
<td>1.81±0.63§</td>
<td></td>
</tr>
<tr>
<td>Fully adjusted†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambulatory arterial stiffness index, units (n=677)</td>
<td>0.043±0.0033</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.025±0.0031</td>
<td></td>
</tr>
<tr>
<td>Adjusted*</td>
<td>0.010±0.005§</td>
<td></td>
</tr>
<tr>
<td>Fully adjusted†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial-ankle pulse wave velocity, m/s (n=333)</td>
<td>1.368±0.094</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.952±0.081</td>
<td></td>
</tr>
<tr>
<td>Adjusted*</td>
<td>0.562±0.144</td>
<td></td>
</tr>
<tr>
<td>Fully adjusted†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values express the change±SE in the arterial indexes associated with 10- or 5-mm Hg increases in systolic or diastolic blood pressure, respectively.

*Adjusted for sex, age, body height, and pulse rate.
†Daytime blood pressure additionally adjusted for nighttime blood pressure and vice versa.
Significance of the effect size: ‡\(P<0.05\); §\(P<0.01\); †\(P<0.001\).

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**Figure 2.** Central augmentation index (CAI), ambulatory arterial stiffness index (AASI), and brachial-ankle pulse wave velocity (baPWV) by quartiles of the daytime (open symbols) and nighttime (closed symbols) systolic blood pressures. Values are mean±SE, adjusted for sex, age, body height, and pulse rate. N indicates the number of subjects. All \(P\) values for trend were significant \((P<0.001)\).
that, among Chinese with normotension on conventional night but not during the day. The key finding of our study was characterized by an elevation of the blood pressure during the day-night difference was smaller than in Irish bank employees (12 mm Hg versus 17 and 19 mm Hg) respectively. Thus, the literature and our previous reports suggested that there might be ethnic diversity in diurnal blood pressure patterns. For instance, Profant and Dimsdale\(^27\) reviewed 18 studies involving 2852 participants. They found that blacks, who were predominantly of African American origin, experienced higher levels of systolic and diastolic blood pressure both at night and during the day. These ethnic differences were significantly greater at night than during the day. In keeping with our present findings, previous studies in Chinese\(^9,28\) showed that nighttime blood pressure dropped by only 2% to 11% of the corresponding daytime levels. In the Ohasama Study,\(^3\) in which the daytime time systolic pressure more accurately predicted cardiovascular mortality and morbidity than the daytime level. In Ohasama residents with 24-hour normotension (mean level: 118/69 mm Hg), each 5% reduction in the nocturnal blood pressure fall resulted in a 15% to 20% higher probability of cardiovascular death.\(^3\) More recently, Ingelsson et al\(^4\) reported that, in elderly Swedish men, each 9-mm Hg increase in the nighttime diastolic pressure entailed a 26% higher risk of congestive heart failure.

Analysis of the International Database

The prevalence of isolated nocturnal hypertension was significantly higher (\(P<0.0001\)) in South Africans of black ancestry (21 of 201 [10.5%]), Japanese (106 of 1038 [10.2%]), and the current population (74 of 677 [10.9%]) than in Western (196 of 3268 [6.0%]) and Eastern (67 of 854 [7.9%]) Europeans. Conversely, the prevalence of isolated daytime hypertension was higher (\(P<0.0001\)) in Western (13.9%) and Eastern (9.1%) Europeans than in South African blacks (6.0%), Japanese (6.6%), and Chinese (4.9%).

Follow-up Study

In 2007, we planned a follow-up study of 43 patients with isolated nocturnal hypertension who lived in 5 centrally located and easily accessible villages. The mean follow-up time was 3.5 years. Of these 43 patients, 2 had a fatal stroke, 2 died from cancer, 1 became demented, 4 had moved out of the study area, and 4 declined to undergo a repeat ambulatory blood pressure recording. Of the 30 participants, 10 (33.3%) developed day-night hypertension, 10 (33.3%) still had isolated nocturnal hypertension, 2 (6.7%) shifted to isolated daytime hypertension, and 8 (26.7%) became normotensive during the day and night.

Discussion

Based on previous observations,\(^9,9-12\) we speculated that there might be a hitherto unrecognized type of hypertension characterized by an elevation of the blood pressure during the night but not during the day. The key finding of our study was that, among Chinese with normotension on conventional measurement, isolated nocturnal hypertension had a prevalence of 13.2% and that isolated nocturnal hypertension was associated with increased arterial stiffness, a sign of intermediate target organ damage. In a follow-up study, we found that a large proportion of patients with isolated nocturnal hypertension either developed day-night hypertension or remained hypertensive only at night.

The association between isolated nocturnal hypertension and increased arterial stiffness is in keeping with previous studies in hypertensive cohorts\(^5-8,26\) or populations,\(^2-4\) which demonstrated that an elevated nighttime blood pressure or a decreased nocturnal fall in blood pressure is associated with target organ damage and a worse cardiovascular prognosis. Indeed, in older patients (\(\geq60\) years) randomly assigned to placebo in the Systolic Hypertension in Europe Trial,\(^2\) nighttime systolic pressure more accurately predicted cardiovascular mortality and morbidity than the daytime level. In Ohasama residents with 24-hour normotension (mean level: 118/69 mm Hg), each 5% reduction in the nocturnal blood pressure fall resulted in a 15% to 20% higher probability of cardiovascular death.\(^3\) More recently, Ingelsson et al\(^4\) reported that, in elderly Swedish men, each 9-mm Hg increase in the nighttime diastolic pressure entailed a 26% higher risk of congestive heart failure.

Analysis of the international database\(^21\) demonstrated that the prevalence of isolated nocturnal hypertension among Chinese, Japanese, and South African blacks was 7.9% in Western (196 of 3268 [6.0%]) and Eastern (67 of 854 [7.9%]) Europeans than in South African blacks (6.0%), Japanese (6.6%), and Chinese (4.9%).
have higher nighttime diastolic blood pressures, possibly because of genetic background, lifestyle, or both.

Although the mechanisms of isolated nocturnal hypertension remain to be elucidated, several pathways might contribute to its pathogenesis. First, in some hypertensive patients, sodium excretion may shift from the day to the night, when sodium-retaining neural and hormonal mechanisms are less activated, and blood pressure can contribute to sodium output.

Indeed, in our study population, we observed a positive relation between the urinary sodium:creatinine ratio and systolic (r = 0.11; P = 0.004) blood pressure at night. Second, alcohol intake is common among JingNing residents (56%). Oral alcohol intake (0.75 to 1.0 g/kg) stimulated sympathetic nerve activity and increased both heart rate and the low:high-frequency ratio of heart rate variability. Non-dippers with a <10% nocturnal decrease in systolic blood pressure compared with dippers showed a reduced fall during the night in the urinary excretion rate of catecholamines.

The above studies might explain why our patients with isolated nocturnal hypertension had increased heart rates at night and suggest that an attenuated withdrawal of sympathetic drive during sleep might contribute to isolated nocturnal hypertension.

The present study has to be interpreted within the context of its potential limitations. First, though we observed that a large proportion of patients with isolated nocturnal hypertension either developed day-night hypertension or remained hypertensive at night in a follow-up study, the short-term reproducibility of isolated nocturnal hypertension remains to be determined. Second, the awake, out-of-bed and asleep, or in-bed blood pressures are usually considered to be the best standards to analyze ambulatory blood pressure recordings in terms of human activity during the day. However, we demonstrated previously that, in the JingNing population, the nighttime blood pressure (10 PM to 4 AM) was, on average, similar, within 0.4-mm Hg systolic and 0.1-mm Hg diastolic, to the asleep blood pressure.

Perspectives

If other studies confirm isolated nocturnal hypertension as a clinical entity, our present findings might have implications for clinical practice, as well as for research on the prognostic significance of the ambulatory blood pressure. Only ambulatory blood pressure measurement who have unexplained target organ damage. Future studies should address the prognostic significance of isolated nocturnal hypertension and determine the outcome benefit of nocturnal blood pressure lowering.

Acknowledgments

The JingNing Study would not have been possible without the voluntary collaboration of the participants and the support of the local public health authorities.

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Disclosures

None.

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