Isolated Nocturnal Hypertension
A Disease Masked in the Dark
Yan Li, Ji-Guang Wang

Hypertension is a hallmark of cardiovascular dysregulation and a major risk factor of cardiovascular disease and mortality.1,2 Treating hypertension by blood pressure-lowering drugs may substantially reduce the risk of cardiovascular events.3,4 Current hypertension guidelines recommend the use of several classes of antihypertensive drugs to bring blood pressure to a defined goal.3–7 However, the control rate of hypertension remains low in treated hypertensive patients in many countries.8,9 Indeed, according to the 2 recent Chinese national blood pressure surveys, only a fourth of treated patients attained the goal blood pressure of 140 mm Hg systolic and 90 mm Hg diastolic.10,11 Even in participants of clinical trials recently conducted in Europe and North America, blood pressure was not controlled in a sizable proportion of hypertensive patients, in spite of free medication and consultation.12,13 For instance, 45% and 26% of participants did not attain the goal blood pressure in the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial, <140/90 or <130/80 mm Hg in diabetes mellitus)12 and ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension, <140/90 mm Hg) trials,13 respectively. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, achieving a systolic blood pressure of 134 mm Hg required on average 2 antihypertensive drugs.14

One of the major reasons for the difficulties in controlling hypertension is the delayed diagnosis. In addition to the low awareness of hypertension owing to the people’s reluctance to measure blood pressure regularly, hypertension can also be masked for technical reasons.15 Ambulatory blood pressure monitoring allows identification of masked hypertension by measuring blood pressure outside doctors’ office, including sleep hours.16 In 2005, we compared daytime and nighttime blood pressure across populations and found that Asians, compared with Europeans, had a smaller nocturnal fall in both systolic and diastolic blood pressures (Figure 1).17 We then identified in our JingNing population study a group of subjects who had abnormally elevated nighttime blood pressure but normal daytime blood pressure, and defined this form of high blood pressure as isolated nocturnal hypertension.18,19 Subsequent studies from us20 and others21 revealed that isolated nocturnal hypertension was prevalent and conferred serious cardiovascular risks. The present review describes several major aspects of isolated nocturnal hypertension.

Definition, Prevalence, and Reproducibility of Isolated Nocturnal Hypertension

Definition
The European hypertension guidelines provided comprehensive guidance on the use of ambulatory blood pressure in the management of hypertension.5 The diagnostic criteria of the European guidelines was therefore used to define ambulatory hypertension in the subjects who did not take antihypertensive medication (Table 1).19

Isolated nocturnal hypertension was defined as a nighttime blood pressure of ≥120 mm Hg systolic or 70 mm Hg diastolic and a daytime blood pressure <135/85 mm Hg; isolated daytime hypertension as a daytime blood pressure of ≥135 mm Hg systolic or 85 mm Hg diastolic and a nighttime blood pressure <120/70 mm Hg; day–night sustained hypertension as a nighttime blood pressure of ≥120 mm Hg or 70 mm Hg diastolic and a daytime blood pressure of ≥135 mm Hg systolic or 85 mm Hg diastolic; and ambulatory normotension as a nighttime blood pressure <120/70 mm Hg and a daytime blood pressure <135/85 mm Hg.19

Prevalence
In a multiethnic international database on ambulatory blood pressure monitoring, the prevalence of isolated nocturnal hypertension was higher in Chinese (10.9%), Japanese (10.2%), and South Africans (10.5%) than in Western (6.0%) and Eastern Europeans (7.9%, Table 2).19

In a Swedish study in 414 patients with type 2 diabetes mellitus, Wijkman et al22 defined isolated nocturnal hypertension as a nighttime blood pressure of ≥120 mm Hg systolic or 70 mm Hg diastolic and a normal clinic (<130/80 mm Hg) and daytime blood pressure (<135/85 mm Hg), and showed that the prevalence of isolated nocturnal hypertension was 3.6% (n=15).

In a scientific presentation on the international 24-hour ambulatory blood pressure monitoring registry, Parati reported that Eastern Asians indeed had higher nighttime blood pressure than Europeans.
Reproducibility

There are no short-term reproducibility data of isolated nocturnal hypertension. We previously studied the long-term reproducibility in a 3.5-year follow-up study of 43 subjects with isolated nocturnal hypertension. Of the 30 patients who underwent a repeated ambulatory blood pressure monitoring, 10 (33.3%) still had isolated nocturnal hypertension, 10 (33.3%) developed day–night sustained hypertension, 2 (6.7%) shifted to isolated daytime hypertension, and 8 (26.7%) became normotensive during day and night. This long-term reproducibility was comparable with the short-term reproducibility of nondipping status between 2 ambulatory blood pressure recordings repeated within 4 weeks. In an analysis in hypertensive patients who enrolled in a placebo-controlled clinical trial and had 2 repeated ambulatory blood pressure recordings 4 to 8 weeks apart, the reproducibility of nocturnal hypertension (≥125/80 mm Hg, κ statistic ≥0.46) was much higher than that of nocturnal nondipping (<5% or <10% of daytime blood pressure, κ statistic ≤0.38).

Table 1. Diagnostic Criteria of Ambulatory Hypertension in Subjects Who Did Not Take Antihypertensive Medication

<table>
<thead>
<tr>
<th>Category of ambulatory blood pressure</th>
<th>Daytime</th>
<th>Nighttime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambulatory normotension</td>
<td>&lt;135/85</td>
<td>&lt;120/70</td>
</tr>
<tr>
<td>Isolated daytime hypertension</td>
<td>≥135/85</td>
<td>&lt;120/70</td>
</tr>
<tr>
<td>Isolated nocturnal hypertension</td>
<td>≥135/85</td>
<td>≥120/70</td>
</tr>
<tr>
<td>Day–night sustained hypertension</td>
<td>≥135/85</td>
<td>≥120/70</td>
</tr>
</tbody>
</table>

Table 2. Prevalence of Isolated Nocturnal and Daytime Hypertension in Various Populations

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Isolated Nocturnal Hypertension (%)</th>
<th>Isolated Daytime Hypertension (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asians</td>
<td>10.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Chinese (n=677)</td>
<td>10.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Japanese (n=1038)</td>
<td>10.5</td>
<td>6.0</td>
</tr>
<tr>
<td>Europeans</td>
<td>7.9</td>
<td>13.9</td>
</tr>
<tr>
<td>East (n=854)</td>
<td>7.9</td>
<td>13.9</td>
</tr>
<tr>
<td>West (n=3268)</td>
<td>6.0</td>
<td>9.1</td>
</tr>
<tr>
<td>South Africans</td>
<td>10.2</td>
<td>6.6</td>
</tr>
</tbody>
</table>

Isolated nocturnal hypertension was defined as a nighttime blood pressure of ≥120 mm Hg systolic or 70 mm Hg diastolic and a daytime blood pressure <135/85 mm Hg; and isolated daytime hypertension as a daytime blood pressure of ≥135 mm Hg systolic or 85 mm Hg diastolic and a nighttime blood pressure <120/70 mm Hg.

Cardiovascular Risk of Isolated Nocturnal Hypertension

Measures of Target Organ Damage

Compared with ambulatory normotensive subjects, patients with isolated nocturnal hypertension had slightly elevated nighttime blood pressure, and more severe target organ damage. Compared with day–night sustained hypertensive patients, they had much lower ambulatory blood pressure but similar target organ damage.

In the JingNing population study, brachial-ankle pulse wave velocity was 16.4 m/s in patients with isolated nocturnal hypertension and 17.3 m/s in patients with day–night sustained hypertension, being significantly higher than that in ambulatory normotensive subjects (14.7 m/s, P<0.05). Central augmentation index, calculated as the ratio of the second to first peak of aortic pressure wave derived from radial pressure waveform and calibrated for brachial blood pressure, was 154.4% in patients with isolated nocturnal hypertension and 147.4% in patients with day–night sustained hypertension, again being significantly higher than that in ambulatory normotensive subjects (134.0%).

The Swedish study in type 2 diabetic patients confirmed the finding in the JingNing population. Fifteen patients with isolated nocturnal hypertension, compared with 45 clinical and ambulatory normotensive patients, had significantly higher diastolic blood pressure (mean±SD 75.9±8.5 mm Hg versus 69.4±9.6 mm Hg; P=0.02) and tended to have higher aortic pulse wave velocity (10.3±2.4 m/s versus 9.3±1.7 m/s; P=0.06) and central systolic blood pressure (116.6±13.9 mm Hg versus 109.8±16.5 mm Hg; P=0.15).

Several other studies defined nocturnal hypertension regardless of daytime blood pressure and isolated nocturnal hypertension in treated hypertensive patients. The results of these studies also suggested that defining nocturnal hypertension might be clinically relevant in terms of target organ damage.

In a study of 223 outpatients who had ambulatory blood pressure monitoring, nocturnal hypertension (nighttime blood pressure ≥120/70 mm Hg), but not nondipping (<10% decline...
in systolic or diastolic blood pressure at night), was associated with the echocardiographically diagnosed left ventricular hypertrophy regardless of antihypertensive therapy. In 82 children and adolescents with type 1 diabetes mellitus, nocturnal hypertension (defined as a nighttime ambulatory blood pressure >95% percentile of the pediatric norms) was associated with increased carotid intima-media thickness.26

In 165 hypertensive patients with well-controlled self-measured blood pressure, isolated nocturnal hypertension (nighttime blood pressure ≥120/75 mm Hg and daytime blood pressure <135/85 mm Hg) was associated with increased carotid intima-media thickness and relative wall thickness.27

**Cardiovascular Disease and Mortality**

The prognosis of isolated nocturnal hypertension was investigated using the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes. This largest ever collaboration of prospective population studies on ambulatory blood pressure monitoring offered the unique opportunity to elucidate the prognostic significance of isolated nocturnal hypertension.28 Indeed, 11 population cohorts from Asia, Europe, and South America included 8711 subjects. During a median follow-up of 10.7 years, 1284 participants died (501 cardiovascular and 742 noncardiovascular) and 1109 experienced a fatal and nonfatal cardiovascular complication (481 stroke and 618 cardiac events). In unadjusted analyses, 577 patients with isolated nocturnal hypertension had a 1-fold higher rate of all-cause and cardiovascular mortality, all cardiovascular events, stroke, and cardiac events (Figure 2).21

After adjustment for cohort, sex, age, body mass index, current smoking, alcohol intake, serum total cholesterol, history of cardiovascular disease, and diabetes mellitus, isolated nocturnal hypertension was still significantly associated with a higher risk of all-cause mortality (hazard ratio [HR] 1.29, 95% CI, 1.01–1.65, \( P = 0.045 \)) and all cardiovascular events (HR 1.38, 95% CI, 1.02–1.87, \( P = 0.037 \)). The HRs for cardiovascular mortality, stroke, and cardiac events had a similar size but did not reach statistical significance mainly because of smaller number of events. Further adjustment for daytime systolic and diastolic blood pressures did not materially change the results.21

Subgroup analyses showed that isolated nocturnal hypertension was particularly relevant in younger subjects for all-cause mortality (HR 1.99, 95% CI, 1.14–3.47) and in nonsmokers (HR 1.78, 95% CI, 1.25–2.55), less obese subjects (HR 1.63, 95% CI, 1.08–2.46), and participants with a history of cardiovascular disease (HR 2.09, 95% CI, 1.00–4.36).21

The prognosis of nocturnal hypertension in treated hypertensive patients was investigated in several studies and summarized in a systematic narrative review. These studies clearly demonstrated the importance of nocturnal hypertension in the management of hypertension. However, defining nocturnal hypertension in subjects with normal clinic blood pressure, especially the isolated form, has quite different clinical implications in the identification and management of hypertension.

**Pathophysiology of Isolated Nocturnal Hypertension**

**General Characteristics**

Because of the prominent across-ethnicity difference in the prevalence of isolated nocturnal hypertension, we postulated that this form of high blood pressure might be a pathophysiologically distinct clinical entity. The correlates of isolated nocturnal hypertension was studied within the JingNing population. In 677 subjects of the JingNing study, if ambulatory normotension or isolated daytime hypertension was chosen as the comparator, patients with isolated nocturnal hypertension tended to be older, had higher serum total and high-density lipoprotein cholesterol and plasma glucose and lower 24-hour urinary sodium excretion, and reported a higher proportion of alcohol intake. If day–night sustained hypertension was chosen as the comparator, patients with isolated nocturnal hypertension also tended to have higher plasma glucose and reported a higher proportion of alcohol intake. However, there was no apparent explanation for the elevated nocturnal blood pressure, such as, for instance, nighttime shift.

In International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes, similar findings were observed for the comparison between isolated nocturnal hypertension and ambulatory normotension.

**Blunted Sodium Metabolism**

According to the pressure-natriuresis mechanism, an elevation in perfusion pressure in the renal artery would lead to a rapid

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**Figure 2.** Cumulative incidence of total mortality (A) and all cardiovascular events (B) by ambulatory blood pressure status. Probability values are for the differences among the 4 categories by log-rank test. Reproduced with permission from Fan et al.21
increase in sodium and water excretion by the kidney. When the dietary sodium intake is too high to be sufficiently excreted by the transiently elevated blood pressure, sustained high blood pressure develops. Because the normal circadian blood pressure rhythm follows a rule of nocturnal dipping from daytime, blood pressure elevation owing to high dietary sodium intake is therefore most likely to initiate in the sleep hours.

Several lines of evidence support the above hypothesis and suggest that isolated nocturnal hypertension may be a consequence of blunted sodium metabolism because of either increased dietary sodium intake or decreased urinary sodium excretion. First, Chinese and Japanese had higher dietary sodium intake and lower dietary potassium intake than other populations. Second, in the JingNing population study, urinary sodium excretion was lower in patients with isolated nocturnal hypertension than the others. Although the mechanism for the lower urinary sodium excretion is unknown, this observation suggests disturbances in sodium metabolism. Third, in a separate study (Zou J, et al, personal communication), we have recently found that sodium dietary intake and renal handling interact to influence predominantly nighttime ambulatory blood pressure.

Arterial Stiffness and Wave Reflections
In the JingNing population study, patients with isolated nocturnal hypertension had similar increased arterial stiffness and wave reflections as day–night sustained hypertension, although the former had much lower 24-hour blood pressure. This finding may suggest reverse causality (ie, isolated nocturnal hypertension as a consequence rather than a cause of increased arterial stiffness and wave reflections). Indeed, in the Swedish study, the only independent differentiator between isolated nocturnal hypertension and ambulatory normotension was aortic pulse wave velocity. There is evidence that arterial stiffness is more closely related to nighttime than daytime blood pressure. It is possible that the effect of arterial stiffness on blood pressure could be unveiled in a condition of low physical activity during sleep.

Obstructive Sleep Apnea Syndrome
Obstructive sleep apnea is a likely cause of isolated nocturnal hypertension. Several but not all previous studies have demonstrated that obstructive sleep apnea is a major cause of nondipping. Nonetheless, there is no study yet directly linking sleep apnea with isolated nocturnal hypertension. This relationship should be investigated in future studies on isolated nocturnal hypertension.

Added Value to Nighttime Dipping: From a Research Phenomenon to a Manageable Disease
Applicability
Already in 1988, O’Brien et al defined dipper and nondipper to describe dipping status of 24-hour ambulatory blood pressure and found that nondippers had a high risk of stroke. Numerous subsequent studies confirmed that nighttime non-dipping was indeed an important cardiovascular risk factor over and above 24-hour mean levels of blood pressure, and even further extended to a more complex concept, which included 4 different categories of 24-hour blood pressure profile, namely dipper, nondipper, extreme-dipper, and reverse-dipper or riser. However, >20 years after the dipping concept has first been published, this topic remains in research. None of the current guidelines recommend clinical use of nighttime blood pressure dipping in the management of hypertension. However, most guidelines clearly recommend diagnostic thresholds for 24-hour, daytime and nighttime systolic and diastolic blood pressures for the diagnosis of hypertension. Isolated nocturnal hypertension is therefore more applicable in the management of hypertension than dipping status.

Reversibility
Isolated nocturnal hypertension can be treated with antihypertensive drugs. It is well-established that, by treating blood pressure to the goal, antihypertensive therapy may reduce the risk of cardiovascular events, such as stroke and coronary heart disease. Therefore, it may be achievable to convince physicians to treat isolated nighttime hypertension and to bring the abnormally elevated nighttime blood pressure to the goal. Of course, antihypertensive drugs may also influence dipping status. However, there is no consistent knowledge, rule, or recommendation on reversing nondipping to dipping while not causing extreme dipping. The elevated nighttime blood pressure confers serious cardiovascular risks and apparently requires proper management. Treating nocturnal hypertension can be an effective and operational therapeutic approach.

Simplicity
Nighttime dipping is complex for several reasons. First, it consists of 4 different categories as mentioned above. Second, systolic and diastolic blood pressures often have contradictory status. Third, it is usually defined by relative differences. However, a night:day ratio of ≥0.9 differs substantially between a nighttime systolic blood pressure of 100 and 130 mm Hg. Isolated nocturnal hypertension has only 2 possible answers (yes or no) and may waive all the complexities of dipping status.

Conclusions and Perspectives
Isolated nocturnal hypertension is prevalent in all populations but more prevalent in Asians than Europeans, suggesting that this form of high blood pressure may be a pathophysiologically distinct clinical entity. It is mild in the elevation of blood pressure but probably not so mild in prognosis. Defining isolated nocturnal hypertension might be clinically relevant for hypertension control and cardiovascular prevention by early identifying and managing those people with normal clinic and daytime ambulatory blood pressure but at high cardiovascular risk. Defining isolated nocturnal hypertension might also be important in the perspective of research, because this form of high blood pressure might be pathophysiologically homogeneous, and can therefore behave as an efficient disease model to study genetic and environmental determinations of blood pressure and cardiovascular phenotypic measurements.

Isolated nocturnal hypertension can only be diagnosed by ambulatory blood pressure monitoring and is therefore largely masked because of the limited use of ambulatory blood pressure monitoring. Future studies should investigate whether
there is any useful marker of isolated nocturnal hypertension. Moreover, this condition should also be studied in the clinical setting to investigate whether treating this disease condition would reduce the risk of cardiovascular disease and mortality and which therapeutic strategy would be effective in treating this form of high blood pressure.

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**Disclosures**

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**References**


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