Association between non-dipper pattern of circadian rhythm of blood pressure (BP) and impaired renal capacity to excrete sodium into urine was confirmed by Bankir et al. in this issue of Hypertension based on a large number of subjects. Although this association has been observed in small studies, their study is the first to show it in a large-scale setting, and, therefore, is highly welcomed.

Because there is a tight link between kidney and hypertension, renal dysfunction causes hypertension, whereas hypertension accelerates renal damage. It is well appreciated that the kidneys play an important role in the long-term regulation of BP. Usually it takes almost 1 week for kidneys to achieve a new steady-state balance of sodium, when sodium intake is altered. Therefore, renal participation in the short-term BP regulation, such as circadian rhythm, has been overlooked. However, the findings of Bankir et al. strongly suggest that nocturnal hypertension and non-dipper pattern of circadian BP rhythm are because of impaired renal capacity to excrete sodium, and circadian BP rhythm is at least in part regulated by kidneys.

Circadian Rhythm of BP and Sodium Sensitivity

Sodium sensitivity of BP is also determined by renal capacity to excrete sodium and is regulated by glomerulotubular balance between glomerular ultrafiltration capability and rate of tubular sodium reabsorption. Thus, sodium sensitivity is increased in chronic kidney disease (CKD) where glomerular filtration rate (GFR) is reduced and also in disorders with enhanced tubular sodium reabsorption, including primary aldosteronism, diabetes mellitus, and metabolic syndrome, where GFR is augmented. When sodium sensitivity is increased, glomerular capillary pressure is usually elevated, resulting in albuminuria and renal damage. It becomes evident that, in patients with high-sodium sensitivity, the nocturnal BP dip is diminished irrespective of the mechanisms causing sodium sensitivity. For example, in both the sodium-sensitive type of essential hypertension and primary aldosteronism, non-dipper patterns of circadian BP rhythm are observed.

Circadian rhythm of urinary sodium excretion rate was compared between 2 groups with different circadian BP rhythms. In dippers, night:day ratios of both BP and sodium excretion were <0.9, even on a high-sodium diet, showing normal circadian rhythms with nocturnal dips. In non-dippers, on the other hand, these ratios were significantly higher than in dippers. Especially, the night:day ratio of sodium excretion was beyond 1 in non-dippers, indicating that urinary sodium excretion was enhanced during the night. Sodium intake restriction significantly lowered the night:day ratios of both BP and sodium excretion in non-dippers, whereas these ratios remained unchanged and <1 in dippers independent of the amount of sodium intake.

There was a strong positive relationship between 2 night:day ratios of BP and sodium excretion on a high-sodium diet but not on low sodium, suggesting that sodium excretion depended on systemic BP on high-sodium intake. It is clear now that, in patients with high-sodium sensitivity of BP, the circadian rhythms of both BP and urinary sodium excretion were all disturbed. Sodium restriction and diuretics restored these rhythms from non-dipper to dipper patterns.

CKD and Circadian BP Rhythm

Because glomerular filtration capability is one of the major factors determining sodium sensitivity, the nocturnal BP dip may be less pronounced as a function of GFR loss. We recently illustrated this quantitative relationship in CKD. As GFR was reduced, night:day ratios of BP, natriuresis, and proteinuria were all increased. Circadian BP rhythm is well known to be shifted to non-dipper in CKD, being consistent with other reports that the rhythm is normalized from non-dipper to dipper after kidney transplantation.

On the other hand, non-dipper pattern is often considered to be a risk factor for the progression of nephropathy. Among young patients with type 1 diabetes, non-dippers frequently progressed to albuminuria and latent nephropathy than dippers. The rate of decline in GFR appears faster in non-dippers than in dippers. It must be further studied which comes first, renal dysfunction or non-dipper. As seen in the link between kidney and hypertension, both renal dysfunction and non-dipper status may be closely associated with each other, leading to renal failure.

Enhanced Tubular Sodium Reabsorption and Nondippers

We showed previously that, in primary aldosteronism, of which the BP was highly sodium sensitive and GFR was augmented because of enhanced tubular sodium reabsorption, the circadian BP rhythm was shifted to non-dipper, whereas it was normalized to dipper by either sodium restriction or removal of adenoma. In diabetes, sodium sensitivity is often increased with augmented GFR, and circadian BP rhythm is disturbed as primary aldosteronism, because sodium is reabsorbed by the proximal tubule with glucose via a sodium-glucose cotransporter. In metabolic syndrome, similarly, high-sodium sensitivity is noted because of enhanced tubular sodium reabsorption, resulting in glomerular hyperfiltration and non-dipper status.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

Correspondence to Genjiro Kimura, Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medical Sciences, Mizuho-ku, Nagoya 467-8601, Japan. E-mail genki@med.nagoya-cu.ac.jp


Hypertension is available at http://hypertension.ahajournals.org
DOI: 10.1161/HYPERTENSIONAHA.108.110213

© 2008 American Heart Association, Inc.
Table. Theoretical Classification of Disorders Causing Nondipper Pattern of Circadian Blood Pressure Rhythm

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disturbance in sleeping rhythm</td>
<td>Sleep apnea</td>
</tr>
<tr>
<td>Disturbance in secretion rhythm of vasoactive hormone</td>
<td>Stroke</td>
</tr>
<tr>
<td>Impaired renal capacity to excrete sodium (sodium-sensitive hypertension)</td>
<td>Day-night shift workers</td>
</tr>
<tr>
<td>Reduced ultrafiltration capability</td>
<td>Cushing syndrome</td>
</tr>
<tr>
<td>Enhanced tubular sodium reabsorption</td>
<td>CKD</td>
</tr>
<tr>
<td></td>
<td>Hypertension in black</td>
</tr>
<tr>
<td></td>
<td>Sodium-sensitive type of essential hypertension</td>
</tr>
<tr>
<td></td>
<td>Primary aldosteronism</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Metabolic syndrome</td>
</tr>
</tbody>
</table>

Orthostatic hypotension must be deleted from this list, because BP is totally dependent on the position of the body rather than circadian rhythm of life.

It is very important to understand, thus, in some conditions with reduced GFR, such as CKD, and the other opposite conditions with augmented GFR by enhanced tubular sodium reabsorption, sodium sensitivity of BP is increased, and circadian BP rhythm is shifted to nondipper status. In this study, Bankir et al.1 speculated that enhanced tubular reabsorption contributed to the genesis of nondippers, because fractional excretion of sodium was lower than the dipper group. However, in people of African origin, fewer nephron numbers may play an important role in creating sodium-sensitive hypertension. Therefore, reduced filtration capability might also contribute to nondipper status.

Disorders Representing Nondippers

In most cases with nondippers, including essential hypertension, CKD, diabetes mellitus, and primary aldosteronism, we believe it evident that renal capacity to excrete sodium is impaired.5 Here is a list of disorders that represent the nondipper pattern of circadian BP rhythm (Table). Before listing, many diseases causing orthostatic hypotension must be excluded from the list of nondippers, because BP is totally dependent on position of the body rather than circadian rhythm of life in orthostatic hypotension. Only a few cases exist in which nondippers are caused by mechanisms other than kidney dysfunction. They are sleep apnea syndrome, stroke, and day-night shift workers, in whom sleeping rhythm itself is disturbed. The others are disorders such as pheochromocytoma and Cushing syndrome, which disturb the secretion rhythm of hormones related to BP regulation.

As I already discussed, renal mechanisms of nondipping are divided into 2 parts: reduced glomerular filtration capability and enhanced tubular sodium reabsorption. When sodium intake is high, the defects in sodium excretory capacity become evident, making BP during night elevated, ie, nondipper, to compensate for diminished natriuresis during daytime and to enhance pressure-natriuresis during night.5 When sodium intake is low, on the other hand, the defects remain latent, allowing BP during night to be lowered, ie, dipper.5

Future Implications

Recently, it has been recognized that renal dysfunction, even to a mild degree, is a strong predictor for future cardiovascular events. In addition, the risk of cardiovascular events is enhanced as renal function deteriorates. However, the precise mechanisms for renal dysfunction to cause cardiovascular events remain unknown. Many investigators have reported that nondippers were exposed to greater risks of cardiovascular complications than dippers. It is also known that high nocturnal BP during sleep has a greater impact on cardiovascular events than daytime and 24-hour average values of BP. Sodium-sensitive subjects, whose circadian BP rhythm is expected to be nondipper,5,6 are also known from our studies to have high risks for cardiovascular events.10 We, therefore, hypothesize that nondipping of BP as a function of GFR loss may be one of the powerful mechanisms causing cardiovascular events in CKD and cardio-renal connection. Further understanding the precise mechanisms of nondipper and the role of the kidneys in the short-term regulation of BP is needed. This field, opened by Bankir et al.,1 may be a key to solving the cardiorenal connection.

Sources of Funding

Supported by Research Grants for Cardiovascular Diseases (C-2001-5) from the Ministry of Health and Welfare of Japan, as well as grants from Salt Science Research Foundation (No. 04C1), Metabolic Disorders Treatment Research Foundation, Japan Cardiovascular Research Foundation, and Grant-in-Aid for Scientific Research (B#19390232) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan through the Japanese Society for the Promotion of Science.

Disclosures

None

References

Kidney and Circadian Blood Pressure Rhythm
Genjiro Kimura

Hypertension. 2008;51:827-828; originally published online March 3, 2008;
doi: 10.1161/HYPERTENSIONAHA.108.110213

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/51/4/827

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/