

# Renal Sodium Handling and Nighttime Blood Pressure

Michel Burnier, MD, FASN, Lionel Coltamai, MD, Marc Maillard, PhD, and Murielle Bochud, MD

---

**Summary:** Blood pressure follows a circadian rhythm with a physiologic 10% to 20% decrease during the night. There is now increasing evidence that a blunted decrease or an increase in nighttime blood pressure is associated with a greater prevalence of target organ damage and a faster disease progression in patients with chronic kidney diseases. Several factors contribute to the changes in nighttime blood pressure including changes in hormonal profiles such as variations in the activity of the renin-angiotensin and the sympathetic nervous systems. Recently, it was hypothesized that the absence of a blood pressure decrease during the nighttime (nondipping) is in fact a pressure-natriuresis mechanism enabling subjects with an impaired capacity to excrete sodium to remain in sodium balance. In this article, we review the clinical and epidemiologic data that tend to support this hypothesis. Moreover, we show that most, if not all, clinical conditions associated with an impaired dipping profile are diseases associated either with a low glomerular filtration rate and/or an impaired ability to excrete sodium. These observations would suggest that renal function, and most importantly the ability to eliminate sodium during the day, is indeed a key determinant of the circadian rhythm of blood pressure.

Semin Nephrol 27:565-571 © 2007 Elsevier Inc. All rights reserved.

**Keywords:** circadian rhythm, renal, dipping, night, blood pressure, cardiovascular complications

---

**B**lood pressure (BP) and heart rate have a definite and reproducible circadian pattern when subjects are evaluated in standardized conditions of life.<sup>1</sup> The highest levels of BP often are measured in the early morning hours; during daytime, blood pressure fluctuates in response to psychologic stresses and physical activities. BP tends to be higher during working hours and lower at home.<sup>2</sup> When subjects go to sleep, BP starts to decrease progressively to reach a trough value during the night. The main determinant of these circadian variations of BP appears to be the activity of the sympathetic nervous system, although several other neurohormonal systems have been shown to follow a circadian rhythm with a peak

in the morning.<sup>1,3,4</sup> This is the case, for example, of plasma cortisol, plasma renin activity, angiotensin II, and aldosterone. Other vascular parameters such as arterial stiffness, vascular resistance, platelet aggregation, and blood viscosity also have a peak in the morning.<sup>1</sup> The BP rhythm may be reversed in subjects working during the night and sleeping during the day, such as in shift workers.<sup>5</sup>

Today the most common way to assess the circadian rhythm of BP is to perform an ambulatory 24-hour BP monitoring. With this method, it became rapidly evident that most individuals have a 10% to 20% decrease in BP when they sleep, but some subjects have only a modest or no decrease in BP during sleep. Occasionally, an increase rather than a decrease in BP is even observed at night. This has led to the classification of subjects into dippers, nondippers (<10% decrease in night BP), extreme dippers (>20% decrease in night BP), or reverse dippers (increase in nighttime BP).<sup>6</sup> This

---

Division of Nephrology and Hypertension Consultation, Department of Medicine, University Hospital, Lausanne, Switzerland

Address reprint requests to Professor Michel Burnier, Service de Néphrologie et Consultation d'Hypertension, Rue du Bugnon 17, CHUV, 1011 Lausanne, Switzerland. E-mail: michel.burnier@chuv.ch

0270-9295/07/\$ - see front matter

© 2007 Elsevier Inc. All rights reserved. doi:10.1016/j.semnephrol.2007.07.007

classification has been criticized because there currently is no consensus on how to define the nocturnal dip (eg, relative versus absolute nocturnal blood pressure decrease, when does the night beginning, and so forth). Moreover, there has been some doubts on the reproducibility of the nocturnal dip of BP in individual patients.<sup>7,8</sup> Thus, according to some investigators, classifying hypertensive patients into dippers or nondippers on the basis of a single ambulatory BP recording may be unreliable and potentially misleading.<sup>7</sup> Indeed, repetition of ambulatory BP measurements in the absence of treatment or during a treatment that had achieved a stable antihypertensive effect was accompanied by a 40% change in the dipping or nondipping pattern.<sup>7</sup> Another limiting factor to the determination of the circadian rhythm of BP using noninvasive BP monitoring is the intermittency of BP measurements that often provides insufficient BP values to determine its variability, particularly during the nighttime period. Yet, variations in the dipping pattern of BP have been reported repeatedly and consistently among certain patients with secondary hypertension and there might be some rational physiologic explanations for the low reproducibility of the dipping, as will be discussed later.

### THE NIGHTTIME DIPPING PATTERN IS ASSOCIATED WITH THE DEVELOPMENT OF CARDIOVASCULAR COMPLICATIONS

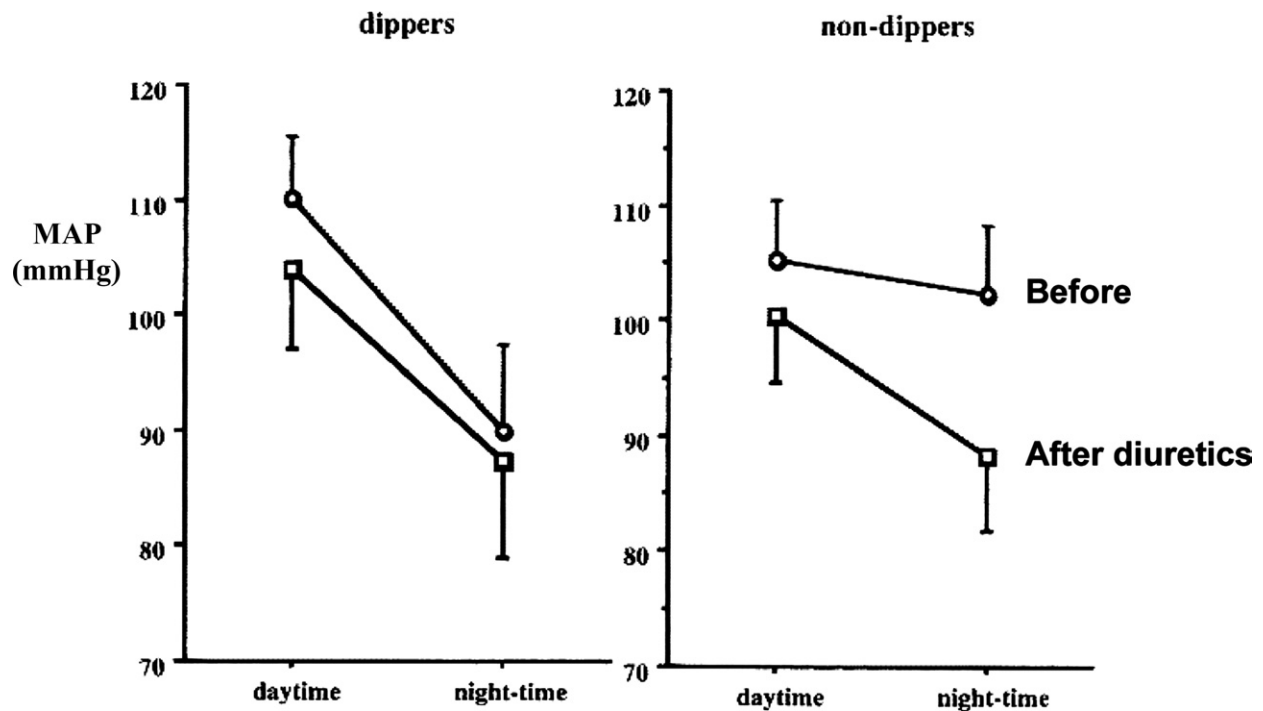
Although the concept still is controversial, evidence has accumulated in recent years suggesting that patients with a blunted overnight decrease in BP are at higher risk to develop target organ damages such as microalbuminuria, chronic renal damage, left ventricular hypertrophy, and cerebrovascular events.<sup>6,9-15</sup> Thus, in young patients with type 1 diabetes without nephropathy, the absence of nocturnal BP dip is associated with an increased risk of microalbuminuria.<sup>11</sup> In a more recent study, Davidson et al<sup>16</sup> showed that the likelihood of doubling serum creatinine or aggravating renal function is markedly higher among patients with a nondipping profile of BP than among dippers. In another large survey performed in 1,057 Swedish men, Bjorklund et al<sup>14</sup> showed that in individuals with diabetes, the nondip-

ping pattern is a sign of poor prognosis as evaluated with surrogate end points of cardiovascular damage (urinary albumin excretion and cardiac size). In a population of Japanese patients aged older than 40 years, 24-hour daytime, and nighttime ambulatory BPs were related linearly and positively with stroke risk.<sup>15</sup> In this study, ambulatory BPs were significantly better related to stroke risk than screening office BP values, but daytime BP was still a better predictor of stroke risk than nighttime BP. Yet, Staessen et al<sup>17</sup> suggested that nighttime BP better predicts cardiovascular risk and mortality than daytime pressures, but this remains somewhat controversial because it was not confirmed in all studies.<sup>18</sup> Of note, an excessive decrease in nighttime BP as seen in extreme dippers is associated with a similar risk of developing multiple silent cerebral infarcts than nondippers or reverse dippers who have a high nighttime BP.<sup>6</sup> This indicates that a decrease in nighttime BP is important to prevent target organ damage, but an excess decrease during the night may be dangerous.

Taken together, these observations suggest that nighttime BP is indeed an important factor that contributes to the development of target organ damage and disease progression. Therefore, it would be important to have a good understanding of the mechanisms that influence the dipping pattern of nighttime BP to provide therapeutic recommendations on how to prevent or correct a nondipping pattern of BP.

### NONDIPPING OF NIGHTTIME BP: DOES THE KIDNEY PLAY A ROLE?

As mentioned previously, several neuroendocrine systems and vascular and hematologic factors follow a circadian rhythm that may contribute to the physiologic day-night variations in BP and circadian rhythm of cardiovascular complications. The renal excretion of water, sodium, and other solutes also has been shown to follow a circadian pattern, with higher excretion rates during daytime than during nighttime.<sup>19</sup> Recently, it was hypothesized that the renal capacity to excrete sodium is an important determinant of the dipping pattern of BP. Thus, in a small group of patients with essential hypertension, Uzu et al<sup>20</sup> showed that sodium restriction using a low-so-



**Figure 1.** Effect of the administration of a diuretic on the dipping pattern of BP in dippers and nondippers. Adapted with permission from Uzu and Kimura.<sup>21</sup>

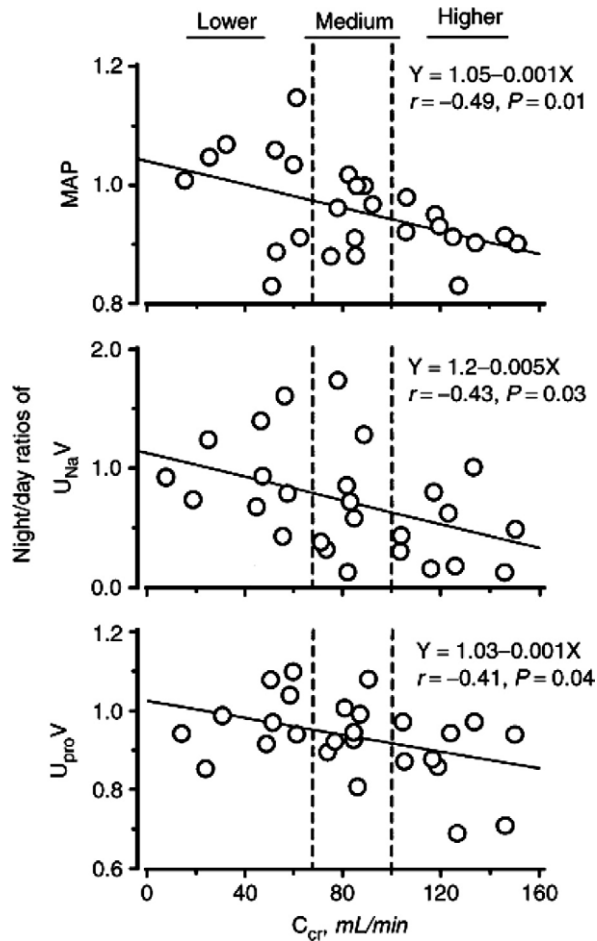
dium diet can shift the circadian rhythm of BP from a nondipper to a dipper pattern. In the same group of patients, the administration of a thiazide diuretic that induces a negative sodium balance also reversed the nondipping pattern of nighttime BP (Fig. 1).<sup>21</sup> Interestingly, the impact of a change in sodium intake was greater among salt-sensitive than salt resistant patients.<sup>22</sup> In a group of 43 untreated hypertensive patients studied on a high sodium intake, we found that 21 patients showed a higher sodium and water excretion during the daytime than during the nighttime and 22 patients showed the reverse pattern. When looking at their changes in nighttime ambulatory BP, we found that the decrease in BP at night was significantly greater in those patients who excreted sodium and water during the daytime than in those excreting water and solutes during the nighttime.<sup>23</sup> These initial observations indicate that the ability to excrete sodium during the daytime is a determinant of nighttime BP at least in the hypertensive population, and particularly among salt-sensitive hypertensive patients.

In a second set of experiments, Fukuda et al<sup>24</sup> investigated the impact of renal function on the night/day ratio of BP and urinary water and elec-

trolyte excretion. Interestingly, they found that in patients with renal diseases and a limited glomerular filtration rate, the lower the glomerular filtration rate the higher the day/night ratio of BP, urinary sodium excretion, and urinary protein excretion (Fig. 2). In this population, Fukuda et al<sup>25</sup> showed that the night/day ratio increases mainly to eliminate sodium and osmoles rather than water. These data emphasize the importance of the glomerular filtration rate, which affects the capacity to excrete sodium as a determinant of nighttime BP and the findings of Uzu et al<sup>20</sup> and Fukuda et al<sup>24,25</sup> recently were summarized in a hypothesis report in which the investigators postulated that the increase in nighttime BP might represent a pressure-natriuresis mechanism whereby sodium balance is maintained in patients with a limited capacity to excrete salt.<sup>26</sup>

### Renal Sodium Handling and BP in the General Population

Yet, whether this mechanism accounts for the nondipping pattern frequently observed in an unselected population has not been shown conclusively to date. In a recent abstract, Mansoor



**Figure 2.** Changes in the night/day ratios of mean arterial pressure, urinary sodium excretion, and urinary protein excretion according to the level of creatinine clearance in patients with chronic kidney diseases. Reprinted by permission from Macmillan Publishers Ltd: Kidney International (2004;65:621-5), copyright 2004.<sup>24</sup>

et al<sup>27</sup> examined the impact of urinary sodium excretion on nighttime ambulatory BP in 69 patients who underwent ambulatory BP monitoring and found that sodium excretion was a determinant of nighttime BP, but only in women. Unfortunately, this group of patients was selected based on the fact that they need an ambulatory BP monitoring and thus may not represent the general population. We recently investigated the association between nighttime BP and the day/night ratio of 24-hour urinary sodium excretion in more than 300 individuals from 73 African families with at least 1 hypertensive subject.<sup>28</sup> In these subjects, divided into tertiles according to their capacity to excrete

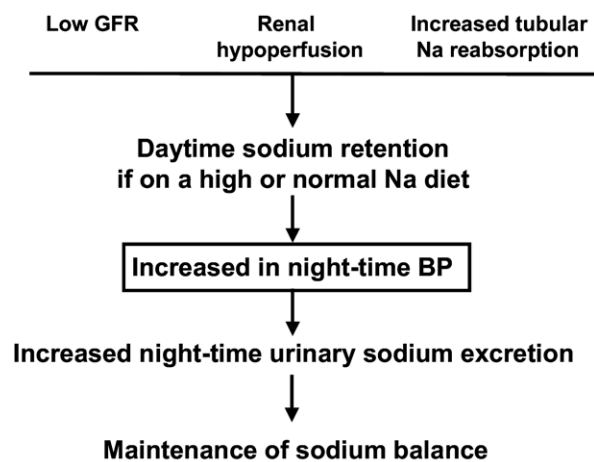
**Table 1. Clinical Situations Associated With a Non-dipping Pattern of BP**

Malignant hypertension
Sleep apnea syndrome
Pheochromocytoma
Toxemia of pregnancy
Cushing's syndrome
Diabetes
Chronic renal failure
Renal and cardiac transplantation
Congestive heart failure
Elderly patients
Drug administration (cyclosporin, nonsteroidal anti-inflammatory drugs)

sodium during the day, we found that those subjects with the lowest daytime excretion of sodium had a higher nocturnal BP and a smaller BP dip at night. These population-based data therefore tend to support the hypothesis according to which the renal capacity to excrete sodium during the daytime determines the level of nighttime BP. Moreover, these data provide some insights on the lack of reproducibility of the dipping pattern in individuals. Indeed, if the nighttime dip is influenced by urinary sodium excretion during the day, the decrease in nighttime BP will depend on the daytime sodium intake, which may vary considerably from day to day. Hence, dietary factors will directly influence the reproducibility of the dipping profile of an individual.

#### ARE THERE CLINICAL DATA SUPPORTING THE ASSOCIATION BETWEEN RENAL SODIUM EXCRETION AND THE DECREASE IN NIGHTTIME BP?

As shown in (Table 1), a nondipping profile of 24-hour BP has been reported in several clinical conditions. These include secondary forms of hypertension such as malignant hypertension,<sup>29</sup> primary hyperaldosteronism,<sup>30,31</sup> Cushing's syndrome,<sup>32</sup> or pheochromocytoma.<sup>32</sup> A blunted decrease in nighttime BP also has been described in patients with a reduced renal function such as patients with diabetic and nondiabetic nephropathies,<sup>24,33-35</sup> congestive heart



**Figure 3.** Potential links between a reduced capacity of excreting sodium during the daytime and a higher nocturnal BP.

failure,<sup>36</sup> organ transplantation,<sup>37-40</sup> or elderly patients. At last, drugs such as cyclosporin and nonsteroidal anti-inflammatory agents have been shown to increase nighttime BP and to blunt the nocturnal dip.<sup>37,41-44</sup> These various clinical conditions share a common feature: they are associated with a reduced capacity of excreting sodium either because of a reduction in glomerular filtration rate (primary or secondary) or because of an increased tubular sodium reabsorption as observed in primary hyperaldosteronism or after the administration of drugs such as nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors,<sup>45</sup> or cyclosporin. Hence, as hypothesized recently by Fukuda et al<sup>26</sup> and presented schematically in Figure 3, the increase in nighttime BP observed in these clinical circumstances may well represent a pressure-natriuresis compensatory mechanism that enables the sodium balance to be restored.

Today, very few if any studies have been conducted to investigate the role of sodium on the circadian profile of BP in those clinical conditions associated with a nondipping profile. If salt intake does indeed determine the magnitude of the BP decrease during the nighttime, specific nonpharmacologic (low-sodium diet) or pharmacologic approaches (diuretics) could be recommended to nondippers to restore a physiologic circadian rhythm of blood pressure and hence decrease their risk of developing cardiovascular complications.

## CONCLUSIONS

BP is known to follow a circadian pattern with a physiologic decrease during the night. To date, little attention has been paid to the nighttime BP for several reasons: the first is that nighttime BP generally is not measured unless a 24-hour recording is performed. Today, with the wider use of ambulatory BP monitoring and the reimbursement of the procedure, physicians are confronted increasingly with the need to provide an interpretation of nighttime BP data. The second difficulty is the definition of normal values of nighttime BP, and the third is the lack of evidence that a specific intervention on nighttime BP provides any clinical benefit for the patient. As a direct consequence of these uncertainties, nighttime BP generally is ignored in clinical practice. Yet, there is now increasing evidence that the level of nighttime BP is important for patients because it contributes to their risk of developing target organ damage or a cardiovascular event. In the present article, we show the actual evidence suggesting that renal function and the capacity to excrete sodium may be important determinants of the nighttime BP and of the BP dip at night, with the increase in nighttime BP representing a pressure-natriuresis mechanism enabling the 24-hour sodium balance to be maintained in individuals. These observations may have some direct clinical implications because sodium restriction and the use of diuretics may help to restore a normal circadian rhythm of BP.

## REFERENCES

1. Smolenski MH, Haus E. Circadian rhythms and clinical medicine with applications to hypertension. *Am J Hypertens.* 2001;14:280S-90S.
2. Pickering TG. Diurnal rhythms and other sources of blood pressure variability in normal and hypertensive subjects. In: Laragh J, Brenner BM, editors. *Hypertension: pathophysiology, diagnosis and management.* Vol I. New York: Raven Press; 1990. p. 1397-405.
3. Portaluppi F, Smolenski MH. Time-dependent structure and control of arterial blood pressure. *Ann NY Acad Sci.* 1996;783:1-342.
4. Baumgart P. Circadian rhythm of blood pressure: internal and external time triggers. *Chronobiol Int.* 1991;8:444-50.
5. Sternberg H, Rosenthal T, Shamiss A, Green M. Al-



- tered circadian rhythm of blood pressure in shift worker. *J Hum Hypertens*. 1995;9:349-53.
6. Kario K, Pickering TG, Matsuo T, et al. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension*. 2001;38:852-7.
  7. Omboni S, Parati G, Palatini P, et al. Reproducibility and clinical value of nocturnal hypotension: prospective evidence from the SAMPLE study. *J Hypertens*. 1998;16:733-8.
  8. Manning G, Rushton L, Donnelly R, Millar-Craig MW. Variability of diurnal changes in ambulatory blood pressure and nocturnal dipping status in untreated hypertensive and normotensive. *Am J Hypertens*. 2000;13:1035-8.
  9. Cuspidi C, Lonati L, Sampieri L, et al. Impact of nocturnal fall in blood pressure on early cardiovascular changes in essential hypertension. *J Hypertens*. 1999;17:1339-44.
  10. Nishimura M, Uzu T, Fujii T, Kimura G. Disturbed circadian rhythm of urinary albumin excretion in non-dipper type of essential hypertension. *Am J Nephrol*. 2002;22:455-62.
  11. Lurbe E, Redon J, Kesani A, et al. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. *N Engl J Med*. 2002;347:797-805.
  12. Ohkubo T, Hozawa A, Nagai K, et al. Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: the Ohasama study. *J Hypertens*. 2000;18:847-54.
  13. Imai Y, Tsuji I, Nagai K, et al. Circadian blood pressure variation related to morbidity and mortality from cerebrovascular and cardiovascular diseases. *Ann NY Acad Sci*. 1996;783:172-85.
  14. Bjorklund K, Lind L, Andren B, Lithell H. The majority of nondipping men do not have increased cardiovascular risk—a population based study. *J Hypertens*. 2002;20:1501-6.
  15. Ohkubo T, Imai Y, Tsuji I, et al. Prediction of mortality by ambulatory blood pressure monitoring versus screening blood pressure measurements: a pilot study in Ohasama. *J Hypertens*. 1997;15:357-64.
  16. Davidson MB, Hix JK, Vidt DJ, Brotman DJ. Association of impaired diurnal blood pressure variation with a subsequent decline in glomerular filtration rate. *Arch Intern Med*. 2006;166:846-52.
  17. Staessen J, Thijs L, Fagard R, et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *Systolic Hypertension in Europe Trial Investigators*. *JAMA*. 1999;282:539-46.
  18. Clement DL, De Buyzere ML, De Bacquer DA, et al. Prognostic value of ambulatory blood pressure recordings in patients with treated hypertension. *N Engl J Med*. 2003;348:2407-15.
  19. Staessen JA, Birkenhager W, Bulpitt CJ, et al. The relationship between blood pressure and sodium and potassium excretion during the day and at night. *J Hypertens*. 1993;11:443-7.
  20. Uzu T, Ishikawa K, Fujii T, et al. Sodium restriction shifts circadian rhythm of blood pressure from non-dipper to dipper in essential hypertension. *Circulation*. 1997;96:1859-62.
  21. Uzu T, Kimura G. Diuretics shift circadian rhythm of blood pressure from nondipper to dipper in essential hypertension. *Circulation*. 1999;100:1635-8.
  22. Uzu T, Kimura G, Yamauchi A, et al. Enhanced sodium sensitivity and disturbed circadian rhythm of blood pressure in essential hypertension. *J Hypertens*. 2006;24:1627-32.
  23. Bankir L, Sellin F, Maillard M, Chiolero A, Burnier M. Influence of moderate body weight excess on the nycthemeral pattern of blood pressure, renal function and sodium and water excretion in patients with essential hypertension. *Arch Mal Coeur Vaiss*. 2004;97:777-81.
  24. Fukuda M, Munemura M, Usami T, et al. Nocturnal blood pressure is elevated with natriuresis and proteinuria as renal function deteriorates in nephropathy. *Kidney Int*. 2004;65:621-5.
  25. Fukuda M, Motokawa M, Miyagi S, et al. Polynocturia in chronic kidney disease is related to natriuresis rather than to water diuresis. *Nephrol Dial Transplant*. 2006;21:2172-7.
  26. Fukuda M, Goto N, Kimura G. Hypothesis on renal mechanism of non-dipper pattern of circadian blood pressure rhythm. *Med Hypotheses*. 2006;67:802-6.
  27. Mansoor GA, Tsimikas JV, Dauser D, et al. Assessment of factors associated with nocturnal blood pressure changes on 2 sessions of ambulatory blood pressure monitoring (The DREAM study) [abstract]. *J Clin Hypertens*. 2006;8 Suppl A:120.
  28. Burnier M, Bochud M, Maillard M, Bovet P. The nycthemeral pattern of urinary sodium excretion is a significant determinant of nighttime blood pressure and of the dipping profile in families of African descent [abstract]. *J Am Soc Nephrol*. 2005;16:176A.
  29. Eguchi K, Kasahara K, Nagashima A, et al. Two cases of malignant hypertension with reversible diffuse leukoencephalopathy exhibiting a reversible nocturnal blood pressure “riser” pattern. *Hypertens Res*. 2002;25:467-73.
  30. Uzu T, Nishimura M, Fujii T, et al. Changes in the circadian rhythm of blood pressure in primary aldosteronism in response to dietary sodium restriction and adrenalectomy. *J Hypertens*. 1998;16:1745-8.
  31. Zacharieva S, Orbetzova M, Elenkova A, et al. Diurnal blood pressure pattern in patients with primary aldosteronism. *J Endocrinol Invest*. 2006;29:26-31.
  32. Zelinka T, Štrauch B, Pecan L, et al. Diurnal blood pressure variation in pheochromocytoma, primary aldosteronism an Cushing’s syndrome. *J Hum Hypertens*. 2004;18:107-11.
  33. Sturrock NDC, George E, Pound N, et al. Non-dipping circadian blood pressure and renal impairment are

- associated with increased mortality in diabetes mellitus. *Diabet Med.* 2000;17:360-4.
34. Goto N, Uchida K, Morozumi K, et al. Circadian blood pressure rhythm is disturbed by nephrectomy. *Hypertens Res.* 2005;28:301-6.
  35. Liu M, Takahashi H, Morita Y, et al. Non-dipping is a potent predictor of cardiovascular mortality and is associated with autonomic dysfunction in haemodialysis patients. *Nephrol Dial Transplant.* 2003;18:563-9.
  36. Goyal D, Macfadyen RJ, Watson RD, et al. Ambulatory blood pressure monitoring in heart failure: a systematic review. *Eur J Heart Fail.* 2005;7:149-56.
  37. van den Dorpel M, van den Meiracker A, Lameris T, et al. Cyclosporin A impairs the nocturnal blood pressure fall in renal transplant recipients. *Hypertension.* 1996;28:304-7.
  38. Taler S, Textor S, Canzanello V, et al. Loss of nocturnal blood pressure fall after liver transplantation during immunosuppressive therapy. *Am J Hypertens.* 1995;8:598-605.
  39. David O, McGregor G, Olsson C, et al. Autonomic dysfunction and ambulatory blood pressure in renal transplant recipients. *Transplantation.* 2001;71:1277-81.
  40. Gatzka CD, Schobel HP, Klingbeil AU, et al. Normalization of circadian blood pressure profiles after renal transplantation. *Transplantation.* 1995;59:1270-4.
  41. Lipkin GW, Tucker B, Giles M, Raine AE. Ambulatory blood pressure and left ventricular mass in cyclosporin and non-cyclosporin treated renal transplant recipients. *J Hypertens.* 1993;11:439-42.
  42. Reitblat T, Zamir D, Estis L, et al. The different patterns of blood pressure elevation by rofecoxib and nabumetone. *J Hum Hypertens.* 2002;16:431-4.
  43. Hermida R, Ayala D, Calvo C, et al. Administration time-dependent effect of aspirin on blood pressure in untreated hypertensive patients. *Hypertension.* 2003;41:1259-67.
  44. Sowers JR, White WB, Pitt B, et al. The effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and type 2 diabetes mellitus. *Arch Intern Med.* 2005;165:161-8.
  45. Rossat J, Maillard M, Nussberger J, Brunner HR, Burnier M. Renal effects of selective cyclooxygenase-2 inhibition in normotensive salt-depleted subjects. *Clin Pharmacol Ther.* 1999;66:76-84.