Non-dipping in hypertension: still a challenging problem

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Many individuals with elevated clinical blood pressure do not develop hypertensive complications and a large number of subjects may be treated with little or no benefit to the individual [1]. A body of evidence suggests that the average of the blood pressure readings recorded during 24 h with ambulatory monitoring is a more powerful predictor of outcome than clinical blood pressure and that it helps identify those subjects who really need antihypertensive treatment [2]. Several attempts have been made to determine whether other parameters derived from 24-h blood pressure recording may add prognostic information to that provided by average ambulatory blood pressure. It is known that blood pressure varies markedly over a 24-h period but the prognostic significance of these changes is still a matter for dispute [3]. In particular, much attention has been paid to the blood pressure changes associated with the sleep–wake cycle. Most individuals have a substantial fall in blood pressure when they sleep accompanied by a decrease in heart rate [4]. These changes are closely linked to the level of arousal. Following the introduction of ambulatory blood pressure monitoring, it appeared that some individuals have little or no fall in blood pressure when they sleep. This has led to classification of subjects into dippers and non-dippers. Whether this classification is associated with adverse outcome has been the subject of much debate [5]. Although the evidence predominantly indicates the presence of a greater cardiovascular morbidity and mortality in non-dippers than dippers, the issue remains, at least in part, controversial due to a number of methodological problems. The main reasons for concern are the poor consistency shown by the diurnal blood pressure rhythm in reproducibility studies [6,7] and the different criteria that have been used in the literature to define dipping/non-dipping status [8,9]. Moreover, the pathogenetic mechanisms of the non-dipping condition are poorly understood, and it is not known whether therapy aiming to improve abnormal diurnal blood pressure rhythm may have a favourable impact on a patient's prognosis [5,8,9].

Effect of physical activity on the diurnal blood pressure rhythm

In this issue of the journal, Cavelaars *et al.* [10] examine how much the overall variance in the sleep–wake blood pressure difference can be accounted for by changes in physical activity. The relationship between ambulatory blood pressures and activity was investigated using reliable methods. Blood pressure was recorded directly through a catheter inserted in the brachial artery and connected to a pressure transducer. Such a technique ensures the reliability of the blood pressure measurement. Physical activity and body posture were measured with five acceleration sensors put on the skin. Lying down, sitting, standing and walking comprised the types of activities taken into account during the recordings, and a strength of the study is that the haemodynamic changes related to the four activities were also studied in the laboratory under supervised conditions. The main finding of the study is that the degree of physical activity during daytime has little influence on the diurnal blood pressure profile and dipping status. This conclusion was based on dippers and non-dippers having similar daytime physical activity, night-time activity and nocturnal decrease in activity. On the other hand, the authors found that blood pressure changes during daytime largely depended on the type of activity. Walking was associated with increased diurnal variation of systolic blood pressure and decreased variation of diastolic blood pressure. By contrast, taking into account only those periods during which subjects were not walking resulted in decreased diurnal variation of systolic blood pressure and increased diurnal variation of diastolic blood pressure. Thus, the proportion of dippers and non-dippers varied greatly according to the blood pressure taken and the period of activity. If the walking period was considered, the proportion of dippers was 81% for systolic blood pressure and 25% for diastolic blood pressure, and was 36 and 53%, respectively, if the non-walking period was considered. This led the authors to conclude that physical activity has a large potential effect on dipping status. These apparently contradictory data deserve further comment. From a pathogenetic standpoint, the results obtained by Cavelaars *et al.* [10] indicate that the dipping phenomenon is not related to the activities performed by a subject during the daytime. If dippers and non-dippers do not differ for degree of physical activity, it means that activity is not the key factor in determining the dipping/non-dipping status. On the other hand, if the diurnal variation in blood pressure is closely related to the type of activity performed during

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the daytime, it follows that, within a single individual, the nocturnal blood pressure fall is heavily dependent on the time spent in each activity. This was previously demonstrated by Mann *et al.* [11] who studied the diurnal rhythm of blood pressure on two different days. Diurnal variations of blood pressure were more pronounced when subjects were active than when they were kept in bed. More recently, the dipping/non-dipping status of 43 subjects was assessed by O'Shea and Murphy [12] using ambulatory blood pressure recorded over two 24-h periods of differing activity levels. In their study, physical activity quantified by electronic activity monitors was an important determinant of dipping status. When ambulatory blood pressure was recorded on a less active day, the proportion of non-dippers trebled, indicating the importance of interpreting 24-h ambulatory blood pressure data only in the presence of adequately quantified activity data. Thus, the conclusion of Cavelaars *et al.* [10] that physical activity performed during ambulatory blood pressure monitoring is clinically irrelevant may be questionable.

Classification of dipping/non-dipping status

The data obtained by Cavelaars *et al.* [10] stress the importance of the choice of blood pressure index (systolic or diastolic) used to define the non-dipping condition. In their study, subjects were defined as dippers if they had a nocturnal fall of systolic or diastolic blood pressure $\geqslant 10\%$ of daytime values. Therefore, subjects who were dippers for systolic blood pressure could be non-dippers for diastolic blood pressure and vice-versa. The last Consensus Conference on ambulatory blood pressure monitoring took into account only systolic blood pressure for the classification of dipping status [8]. This definition has been used by most authors on the basis that a non-dipping pattern is more often observed for systolic than for diastolic blood pressure [13,14]. According to some authors, both the systolic and the diastolic nocturnal blood pressure reductions should be abnormal for the definition of non-dipper [12]. Others have used mean blood pressure for the classification [15]. Using systolic and diastolic blood pressures separately for the classification of dipping status and then pooling the subjects, as performed by Cavelaars *et al.* [10], may explain why activity did not vary according to dipping status in their study. In fact, more time spent walking increased the proportion of 'systolic' dippers, whereas more time spent in non-walking activities increased the proportion of 'diastolic' dippers. It is likely that physical activity would differ between dippers and non-dippers if only systolic blood pressure were taken into account. As the authors themselves concede, these data show that different results can be obtained according to the blood pressure index used for the definition of dippers and non-dippers. This calls for adhering to common procedures for the classification of dipping status.

Night-time activity and quality of sleep

In agreement with previous reports [15], in the study by Cavelaars *et al.* [10], increased night-time activity did influence the diurnal rhythm causing a smaller nocturnal reduction of systolic blood pressure. Sleep disturbances that might lead to arousals have been suggested as a possible causative mechanism for the higher levels of sleep activity in non-dippers [15]. For example, patients with sleep apnoea are more likely to have a non-dipping blood pressure profile than patients without sleep apnoea [16]. According to Cavelaars *et al.* [10], sleep quality assessed by a questionnaire did not affect the day–night blood pressure difference and was not correlated with nocturnal activity. However, the procedure used to assess the quality of sleep appears to be a limitation of the study. One study using a more objective method to identify sleep showed that hypertensive dippers spent more time in bed asleep than non-dippers, and that a non-dipper blood pressure profile can indeed be due to increased activity during sleep [15]. Several factors may contribute to disturbed sleep in non-dippers [17]. Sleep apnoea may be a possible causative factor and, in a study of patients with obstructive sleep apnoea, 84% had a non-dipper blood pressure profile [18]. In addition, less clinically evident disturbances of sleep including snoring and mild apnoeas may cause nocturnal elevations in blood pressure [19,20]. Increases in blood pressure during apnoeic episodes have been attributed to increased sympathetic activity, as shown by studies measuring muscle sympathetic nervous activity [21]. This mechanism may explain the selective increase in systemic vascular resistance found by Cavelaars *et al.* [10] in their subjects with a non-dipper blood pressure pattern. Sleep disturbances have been found to be more frequent in overweight or obese subjects [22], and the non-dippers studied by Cavelaars *et al.* [10] indeed had a higher, although non-significant, body mass index compared to dippers. An alternative explanation for the higher degree of activity during sleep in non-dippers is that repeated cuff inflation may interfere with sleep, meaning that they would suffer a higher degree of sleep interference.

Diurnal variation of systemic vascular resistance: non-dipping or non-peaking?

There is general agreement that the nocturnal fall in blood pressure is mostly due to a decrease in cardiac output driven by the pronounced decrease in heart rate, and the data obtained by Cavelaars *et al.* [10] are in line with previous reports. There is less agreement regarding the diurnal variation of total peripheral resistance, which was found to be lower during sleep in some studies [23] but higher in others [24]. However, the

behaviour of vascular resistance is not uniform across a given sample. In some subjects, peripheral resistance can be higher during sleep and, in others, higher during wakefulness [24]. In the study by Cavelaars *et al*. [10], systemic vascular resistance calculated from the intra-arterial blood pressure waveforms showed a different diurnal variation in dippers and non-dippers. In dippers, peripheral resistance did not change significantly from day to night, whereas it significantly increased in non-dippers. The discrepant results obtained in the two groups cannot be attributed to a different response to the change in posture from day to night because daytime supine rest in the laboratory caused a small comparable decline in peripheral resistance in the two groups. As mentioned previously, a possible explanation for the nocturnal increase in peripheral resistance in non-dippers is a heightened sympathetic activity during sleep, which may be the consequence of sleep-disordered breathing syndromes. However, as noted by Pickering and James [25] a decade ago, the problem could be seen from a different standpoint. A persuasive case has been made for taking sleep blood pressure as the baseline level for analysis of the 24-h rhythm. Sleep blood pressure is less affected by environmental factors, and could thus conceivably be taken as the 'basal' blood pressure of an individual. In most individuals, sympathetic tone is lower during sleep than during wakefulness and can be considered as being at a 'floor' level [26]. According to this view, subjects with greater day/night blood pressure difference might be classified as 'peakers' [25]. A recent study by Narkiewicz *et al*. [27] measuring muscle sympathetic nerve activity showed that subjects with higher daytime resting measurements of sympathetic traffic had a more striking day–night difference in systolic blood pressure than subjects with smaller sympathetic activity. Raikkonen *et al*. [28] found blunted cardiovascular responses to daily activities in non-dippers compared to dippers. This indicates that dippers (or peakers) are characterized by higher sympathetic tone during wakefulness, possibly accounting for the absent decrease in peripheral resistance from night to day observed in dippers by Cavelaars *et al*. [10]. The results obtained by Hojo *et al*. [29] with power spectral analysis of the R–R interval are in agreement with this concept. In their study, the mean daytime LF/HF power ratio was significantly lower in non-dippers than in dippers, whereas the night-time LF/HF power ratio was not significantly different between the two groups. During head-up tilting test, the LF/HF power ratio increased significantly in dippers whereas there was no significant change in the LF/HF power ratio in non-dippers. These results suggest that impaired night to day modulation in autonomic nervous system activity could account for the altered diurnal variation of peripheral resistance and the inadequate blood pressure increase during the daytime in non-dippers (non-peakers).

In conclusion, the study by Cavelaars *et al*. [10] provides further insight into the mechanisms of the diurnal blood pressure rhythm. The authors have yielded several interesting observations concerning the role of physical activity in modulating the wake–sleep cycle. However, their findings do not provide a definite answer to the question of whether the non-dipping phenomenon should be interpreted as an impaired capacity to reduce blood pressure at night or as a reduced response to physical and/or mental stimuli during daytime. A better understanding of the mechanisms underlying the altered diurnal blood pressure rhythm in hypertensive non-dippers would help to establish whether and how a non-dipping pattern should be treated with the purpose of restoring a normal rhythm.

References

1 Leitschum M, Cupples LA, Kannel W, Gagnon D, Chobanian A. High normal blood pressure progression to hypertension in the Framingham study. *Hypertension* 1991; **17**:22–27.

2 Guidelines Committee: European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; **21**:1011–1053.

3 Mancia G, Grassi G. Mechanisms and clinical implications of blood pressure variability. *J Cardiovasc Pharmacol* 2000; **35 (suppl 4)**: S15–S19.

4 O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, *et al*. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003; **21**:821–848.

5 Morgan TO. Is non-dipping status a predictor of cardiac morbidity? *J Hypertens* 2002; **20**:1469–1471.

6 Palatini P, Mormino P, Canali C, Santonastaso M, De Venuto G, Zanata G, *et al*. Factors affecting ambulatory blood pressure reproducibility: results of the HARVEST trial. *Hypertension* 1994; **23**:211–216.

7 Omboni S, Parati G, Palatini P, Vanasia A, Muiesan ML, Cuspidi C, *et al*. Reproducibility and clinical value of nocturnal hypotension: prospective evidence from the SAMPLE study. Study on Ambulatory Monitoring of Pressure and Lisinopril Evaluation. *Hypertension* 1998; **16**:733–738.

8 Staessen JA, Asmar R, De Buyzere M, Imai Y, Parati G, Shimada K, *et al*. Task Force II: blood pressure measurement and cardiovascular outcome. *Blood Press Monit* 2001; **6**:355–370.

9 Verdecchia P. Using out of the office blood pressure monitoring in the management of hypertension. *Curr Hypertens Rep* 2001; **3**:400–405.

10 Cavelaars M, Tulen JHM, van Bemmel JH, van den Meiracher AH. Physical activity, dipping and haemodynamics. *J Hypertens* 2004; **22**:2303–2309.

11 Mann S, Millar-Craig MW, Melville DI, Balasubramanian V, Raftery EB. Physical activity and the circadian rhythm of blood pressure. *Clin Sci* 1979; **57 (suppl)**:291S–294S.

12 O'Shea JC, Murphy MB. Nocturnal blood pressure dipping: a consequence of diurnal physical activity blipping? *Am J Hypertens* 2000; **13**:601–606.

13 Staessen JA, Bieniaszewski L, O'Brien E, Gosse P, Hayashi H, Imai Y, *et al*. Nocturnal blood pressure fall on ambulatory monitoring in a large international database. The 'Ad Hoc' Working Group. *Hypertension* 1997; **29**:30–39.

14 Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, *et al*. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension* 1994; **24**:793–801.

15 Mansoor GA. Sleep actigraphy in hypertensive patients with the 'non dipper' blood pressure profile. *J Hum Hypertens* 2002; **16**:237–242.

16 Suzuki M, Guilleminault C, Otsuka O, Shiomi T. Blood pressure 'dipping' and 'nondipping' in obstructive sleep apnea syndrome patients. *Sleep* 1996; **19**:382–387.

17 Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000; **342**:1378–1384.

18 Loredo JS, Ancoli-Israel S, Dimsdale JE. Sleep quality and blood pressure dipping in obstructive sleep apnea. *Am J Hypertens* 2001; **14**:887–892.

19 Noda A, Yasuma F, Okada T, Yokota M. Influence of movement arousal on circadian rhythm of blood pressure in obstructive sleep apnea syndrome. *J Hypertens* 2000; **18**:539–544.
20 Amin RS, Carroll JL, Jeffries JL, Grone C, Bean JA, Chini B, *et al*. Twenty-four-hour ambulatory blood pressure in children with sleep-disordered breathing. *Am J Respir Crit Care Med* 2004; **169**:950–956.
21 Winnicki M, Palatini P. Obstructive sleep apnoea and homocysteine: an overview. *Eur Heart J* 2004; **25**:1281–1283.
22 Narkiewicz K, van de Borne PJ, Cooley RL, Dyken ME, Somers VK. Sympathetic activity in obese subjects with and without obstructive sleep apnea. *Circulation* 1998; **98**:772–776.
23 Khatri IM, Freis ED. Hemodynamic changes during sleep. *J Appl Physiol* 1967; **22**:867–873.
24 Mehta SK, Walsh JT, Goldberg AD, Topham WS. Increasing daytime vascular resistance with progressive hypertension in ambulant patients. *Am Heart J* 1987; **113**:156–162.
25 Pickering TG, James GD. Determinants and consequences of the diurnal rhythm of blood pressure. *Am J Hypertens* 1993; **6**:166S–169S.
26 Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. *N Engl J Med* 1993; **328**:303–307.
27 Narkiewicz K, Winnicki M, Schroeder K, Phillips BG, Kato M, Cwalina E, *et al*. Relationship between muscle sympathetic nerve activity and diurnal blood pressure profile. *Hypertension* 2002; **39**:168–172.
28 Raikkonen K, Matthews KA, Kondwani KA, Bunker CH, Melhem NM, Ukoli FA, *et al*. Does nondipping of blood pressure at night reflect a trait of blunted cardiovascular responses to daily activities? *Ann Behav Med* 2004; **27**:131–137.
29 Hojo Y, Noma S, Ohki T, Nakajima H, Satoh Y. Autonomic nervous system activity in essential hypertension: a comparison between dippers and non-dippers. *J Hum Hypertens* 1997; **11**:665–671.