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REVIEW

Causes and consequences of a non-dipping blood pressure profile

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ABSTRACT

The development and clinical application of ambulatory blood pressure monitoring (ABPM) has brought several of the main features of the circadian blood pressure (BP) rhythm to light. ABPM has shown to be a very useful method in cardiovascular risk assessment and remains the only method of diagnosing a non-dipping blood pressure profile. A 'non-dipping' BP profile is currently regarded as a risk factor in its own right for cardiovascular (CV) events and target organ damage. Nevertheless, the reliability of ABPM in assessing dipping status is still being questioned. Furthermore, a clear-cut definition of 'non-dipping' has not been established so far. The pathophysiological mechanism(s) of a non-dipping profile might involve abnormalities in extracellular volume and/or vascular resistance regulation. In addition, differences in daytime and nighttime activity, sleep quality and body position during sleep are involved as well. A reduction in cardiovascular risk by a pharmacologically induced switch from a non-dipper to a dipper status might be expected, but remains to be proven.

KEYWORDS

ABPM, non-dipping, hypertension, circadian

INTRODUCTION

Since the development and clinical application of ambulatory blood pressure monitoring (ABPM), various studies have shown that assessing the circadian blood pressure (BP) profile is more predictive than office BP readings in estimating cardiovascular (CV) risk.[1-3] A special advantage of ABPM as compared with all other forms of BP measurements is that information is obtainable about BP during the night. Compared with daytime values BP in most subjects is considerably lower during the night and the attenuation of this physiological nocturnal decline should be regarded as abnormal.[4] Besides being of interest for research purposes, the clinical relevance of this abnormality relates to its close association with hypertensive target organ damage, its increased risk for future CV events and its association with clinical conditions such as certain secondary forms of hypertension, renal function impairment and disturbances of the autonomic nervous system.[5-16] Of note, a non-dipping profile in some circumstances might be favourable. For instance in non-dipping patients with an already challenged cerebral perfusion, a medically induced nocturnal BP lowering may induce hypoperfusion in that area.[17]

In this overview we first go into the definition and reproducibility of a non-dipping BP profile, then we describe possible mechanisms and finally we discuss its clinical relevance.[18]

DEFINITION

A 'non-dipping BP profile' is usually defined as a nocturnal BP fall of less than 10%. This definition requires further clarification.

First of all, should one look at systolic BP (SBP) alone, or should diastolic BP (DBP) and/or mean arterial pressure (MAP) be taken into account as well?

The effect of physical activity on SBP and DBP is unequal. With increased levels of activity there is an almost linear increase in SBP, whereas DBP tends to decrease. So, dipping classification may vary with the BP index taken.[19] Most monitors used for ABPM measure BP oscillometrically. With this technique MAP, rather than SBP or DBP, is assessed most accurately. It might be

proposed, therefore, to use MAP as the BP index for classification of dipping status.

Secondly, arguments can be raised that in the definition, 'nocturnal' should be substituted with 'sleeping'. The process of BP dipping is not likely to occur when a person does not sleep at night. Nightshift workers exemplify this. During the first 24-hour period of the nightshift, a dipping pattern switches to a non-dipping pattern. Gradually, the non-dipping pattern changes back to a dipping pattern during the following days. The BP dip in these subjects is then seen during their daytime sleeping period.[20,21] To define the sleeping period, various (combinations of) methods are available. A simple method is to use diary card entries. Some prefer a short fixed time period to define nighttime, for instance from midnight to 6 am, thereby excluding to a large extent overlapping periods that patients may be either awake or have gone to bed.[22] The morning BP surge will be excluded when this latter method is chosen. Since non-dippers have a rather modest morning BP surge as compared with dippers,[23] this will only be of minor consequence for their nocturnal dipping percentage. Nevertheless, subjects classified as (borderline) dippers by the use of other methods might be classified as non-dippers with this method. A more recent method is the use of activity and posture monitoring, which is highly accurate, especially when combined with the diary card entry method.[19]

Finally, where does the 10% cut-off point come from, and why should a binary distribution be favoured over a continuous one? In our literature search we found no evidence of the 10% cut-off being more discriminative than other neighbouring cut-off points. Although arbitrary, the 10% cut-off is easy to use and seems to be quite practical so far.[24]

REPRODUCIBILITY

The clinical usefulness of a non-dipping BP pattern obviously depends on its reoccurrence from one occasion to another. Unfortunately, this is not always the case. For instance, a study by Manning *et al*. showed that only 54% of 79 untreated hypertensives and normotensives could be consistently classified as dippers, after performing three ABPMs within six months.[25] In another study, in which two ABPMs were performed separated by more than one year in 170 hypertensives, no less than 40% had changed their dipping status. It should be remarked that although recordings were performed while patients were off antihypertensive treatment, between the two measurements subjects were treated with BP-lowering medication.[26] A recent study showed more promising results in reproducibility.[27] Sixty-five recently diagnosed untreated hypertensives underwent repeated ABPM. The nocturnal dipping pattern remained unchanged in 82% of the patients; 12% converted from a non-dipping to a dipping status after the repeated measurements. Also in studies in which physical activity during the day was observed more objectively, dipping status seemed to be more reproducible.[28,29] A possible explanation is that subjects have a greater tendency to behave according to study protocol than when their activity is only controlled by a diary. They are also more likely to behave approximately the same during subsequent ABP measurements.

Change in body position from one night to another potentially affects reproducibility.[30] When subjects are lying on their side rather than on their back, it can make a difference of about 12 to 14 mmHg if the cuff is attached to the upper arm or the forearm.[31,32] Measurement of arm position during ABPM is possible with activity and posture monitoring systems. Using these systems correction of effects of changes in arm position during repeated recordings is possible. However, in a small study correcting for changes in body position during the night did not improve the reproducibility of dipping status.[33]

In conclusion, reproducibility of dipping or non-dipping status is not perfect. Classification of dipping status and its reproducibility can be improved when measurements are done on like days, when daytime activity and duration of nighttime bed rest are objectively observed and when changes in the position of the cuffed arm during the night are taken into account.

PROPOSED MECHANISMS

Inactivity and sleep are the two factors explaining the normally occurring nocturnal decline in BP. It might be argued, therefore, that daytime inactivity and poor sleep quality contribute to a decrease in this decline. For instance, it has been suggested that subjects with a more pronounced risk of CV events may be more likely to be more inactive during the day and therefore are also more prone to be diagnosed as non-dippers.[34]

Although daytime inactivity and poor sleep quality may explain the non-dipping phenomenon, contradictory arguments can be given as well. First, in studies comparing dippers and non-dippers daytime BP in both groups is usually similar.[16] Second, non-dipping also occurs in patients with good sleep quality according to their diary input.[19] Third, as summarised in *table 1*, non-dipping is related to a number of clinical conditions that usually have no influence on daytime activity and/or sleep quality.

Concerning the underlying haemodynamics, a normal dipping pattern is mainly due to a decrease in cardiac output (CO), whereas nighttime systemic vascular resistance (SVR) remains similar to daytime SVR or is even increased.[33,35] The nocturnal decrease in CO is mainly

Table 1. *Associated conditions and other influences*

Endocrine conditions	Renal dysfunction	Disturbances of the autonomic nervous system	Miscellaneous
Aldosteronism [5-10]	Chronic kidney damage [11-14]	Pure autonomic failure [57-60]	Salt-sensitive hypertension [42,44,61,62]
Hypercortisolism [63,64]	Renal transplantation [12,18*]	Diabetic neuropathy [65-67]	Pre-eclamptic toxaemia [68]
Pheochromocytoma [69]	Unilateral nephrectomy [53]	Uraemic neuropathy [12]	Malignant hypertension [70]
Acromegaly [71]		Familial amyloidotic polyneuropathy [72]	Cardiac transplantation [73,74*]
Hyperthyroidism [75]		Obstructive sleep apnoea syndrome [76]	Ethnicity [77**]
Hyperparathyroidism [78]			Disturbances in circadian plasma melatonin changes [79]

*** Use of immunosuppressive therapy may play a role as well.[80,81] ** People of African ancestry have a higher prevalence of non-dipping than Caucasians.**

caused by a decrease in heart rate (HR), with stroke volume compared with daytime values remaining unchanged.[35] A few studies have compared the day-night changes in CO and SVR in dippers and non-dippers.[19,33,36-41] The findings of these studies are not uniform. Thus a non-dipping profile might be caused by a diminished nocturnal decrease in CO, an exaggerated increase in SVR or a combination of these factors. An important reason for these discrepant findings is that the diurnal variation of CO and SVR, unlike BP, is strongly influenced by diurnal changes in posture and daily activity.[19]

Looking at conditions associated with non-dipping may be helpful in explaining its underlying mechanism. Autonomic dysfunction is almost always associated with a non-dipping BP profile and sometimes even with nocturnal hypertension.[15,16] Due to impairment of the sympathetic nervous system (SNS), an excessive volume of blood will be pooled in the lower part of the body when assuming the upright position. In addition, the kidneys retain fluid retention during the day, which is related to a low renal perfusion pressure. When assuming the horizontal position this pooled blood is remobilised, causing an increase in stroke volume and CO and hence in BP, which cannot be counteracted by the baroreflex due to an impaired autonomic function. The observation that impaired renal function, hyperaldosteronism and hypercortisolism are frequently associated with non-dipping supports the role of excessive extracellular fluid volume in the pathogenesis of non-dipping. This is further substantiated by studies showing that in sodium-sensitive hypertensives a non-dipping BP can be converted to a dipping BP profile with a sodium-restricted diet or use of diuretics.[42,43] Although one study shows that the opposite can also occur.[44]
In patients with the obstructive sleep apnoea syndrome and pheochromocytoma, a relatively high sympathetic tone or an increased concentration of circulating catecholamines are likely operative in the non-dipping BP pattern observed with these conditions. We suggest that in these conditions, both an inappropriate nocturnal increase in venous and arterial tone explain the non-dipping BP pattern.

RELEVANCE

The clinical relevance of establishing a non-dipping BP pattern lies in its proven association with more severe hypertensive target organ damage and its improved prediction of an increased CV risk, not only in hypertensive, but also in normotensive subjects.[45-49] Left ventricular hypertrophy, carotid intima-media thickening, microalbuminuria and cerebrovascular diseases are much more prevalent in non-dippers than in dippers.[1,4,50-52]

Furthermore, it is well recognised that a non-dipping BP pattern is associated with renal function impairment.[11-14,53] Conversely, limited evidence indicates that such a pattern also accelerates the progression of renal dysfunction.[54-56]

CONCLUSIONS

A non-dipping BP pattern has been well established as an entity with potentially important clinical implications. Although a nocturnal BP decline of less than 10% compared with daytime values is usually regarded as indicative for the diagnosis of non-dipping, it should be remarked that this threshold is arbitrary. In addition, it is not well settled which index of BP, i.e. SBP, DBP, MAP or some combination of these indexes, should be used. On theoretical grounds, we have argued to base the diagnosis on a less than 10% nocturnal decline of MAP.
An unsolved problem is the imperfect reproducibility of a non-dipping status. Taking into account daytime and nighttime physical activity and subjective sleep quality and performing recordings on like days, reproducibility can almost certainly be improved. The mechanism underlying a non-dipping BP profile remains unknown

in many instances. Evidence is accumulating that volume-related factors are frequently involved. This explains the association of non-dipping with salt-sensitive forms of hypertension, renal function impairment and mineralocorticoid-induced forms of hypertension. How this volume dependency of BP translates into a non-dipping BP pattern requires further investigation.

Until the present day, there are still no specific therapeutic recommendations based on dipping status. As discussed, there is limited evidence that with certain antihypertensive agents, for instance diuretics, or changing the timing of drug administration, a non-dipping BP pattern can be reversed into a dipping pattern. Whether CV outcome improves by changing the dipping status pharmacologically remains to be proven.

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