Hypertension

REVIEW

Pathophysiology of the Nondipping Blood Pressure Pattern

Justine Huart*, Alexandre Persu*, Jean-Philippe Lengelé, Jean-Marie Krzesinski, François Jouret, George Stergiou

ABSTRACT: The nondipping blood pressure (BP) pattern corresponds to a disruption in the circadian BP rhythm with an insufficient decrease in BP levels during night-time sleep as observed using 24-hour ambulatory BP monitoring. Patients with nondipping BP pattern have poorer renal and cardiovascular outcomes, independent of their average 24-hour BP levels. The pathophysiology of nondipping BP is complex and involves numerous mechanisms: perturbations of (1) the circadian rhythm, (2) the autonomic nervous system, and (3) water and sodium regulation. This review provides an outline of the pathways potentially involved in the nondipping BP profile in different conditions. A recent hypothesis is also discussed involving the role of gut microbiota in the dipping/nondipping patterns, via the fecal diet-derived short chain fatty acids.

Key Words: diurnal rhythm ■ hypertension ■ microbiota ■ nocturnal ■ nondipper ■ pathophysiology

In healthy humans, arterial blood pressure (BP) exhibits a circadian rhythm,[1] which has been well demonstrated using 24-hour ambulatory blood pressure monitoring.[2,3] In healthy conditions, BP declines during night-time sleep by 10% to 20%. This nocturnal decrease is called normal dipping and an individual with such a pattern is classified as a dipper (Figure 1A). The evaluation of the BP circadian rhythm of an individual on the basis of a single 24 hour-ambulatory blood pressure monitoring recording remains imperfect, with a level of reproducibility quantified at 8.3/5.6 mm Hg for systolic/diastolic BP[4] and around 25% of patients can be observed to exhibit a change in dipping status from one 24 hour-ambulatory blood pressure monitoring session to the next.[5,6] The following problems are associated with this lack of reproducibility: a relatively small number of readings used to define awake/asleep BP, differences in the individuals' day-to-day physical and mental activities and in the quality of the sleep (as the cuff inflation may cause arousals), as well as the definition of day/night-time intervals used in studies: for example, arbitrary fixed-narrow time intervals, versus patient reported in-bed/out-of-bed intervals, versus true awake/asleep intervals defined by actigraphy.[1,7–9]

When the nocturnal decrease in BP during sleep is blunted or lost (ie, <10% of daytime BP level), this is called nondipping, and these individuals are classified as nondippers(Figure 1B), a concept first introduced by O'Brien et al[2,3,10] in 1988. When the nocturnal BP during sleep rises above the awake levels, this is called reverse dipping and the individuals are classified as reverse dippers or risers[2,3,11] (Figure 1C). Patients with nondipper and riser BP pattern have more severe target organ damage and poorer renal and cardiovascular outcomes than dippers.[12–15] Increased cardiovascular morbidity is independent of the overall BP load during a 24-hour period[1,16–18] but seems to be linked with nocturnal hypertension.[19] Indeed, it has been shown that night-time BP is the most potent predictor of cardiovascular mortality.[20,21]

When the nocturnal decrease in BP is exaggerated (ie, >20% of daytime BP level), this is called extreme dipping (Figure 1D). Whether or not extreme dippers have a worse cardiovascular prognosis than dippers is still debated.[22] At the end of night-time sleep, at the wake-up time, BP increases sharply, which is called morning surge (Figure 1D). The morning surge in BP may also predict the occurrence of cardiovascular events, especially when it is >55 mm Hg in the elderly.[23–25]

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Nonstandard Abbreviations and Acronyms	
BP	blood pressure
OSAS	obstructive sleep apnea syndrome

Nocturnal hypertension and morning BP surge have therefore been proposed as new targets for the prevention of organ damage and cardiovascular events.[20,26] Accordingly, unraveling the pathophysiology of the nondipping BP profile may help in improving the management of these patients. Still, the mechanisms underlying these variations are complex. The present review aims to discuss the underlying mechanisms, with emphasis on pathological conditions frequently associated with nondipping. Finally, we will expose some hypothetical mechanisms requiring further investigations.

CONDITIONS ASSOCIATED WITH NONDIPPING

The percentage of nondippers in patients with essential hypertension has been estimated as 25%.[27] Patients with secondary hypertension present with a nondipping BP profile more frequently than those with essential hypertension, possibly due to the fact that most patients with secondary causes have severe hypertension[28,29] as the severity of hypertension, irrespective of its etiology, is related to the nondipping pattern.[30] This is mostly the case for patients with pheochromocytoma, but also for patients with renal or renovascular hypertension, as well as endocrine causes of hypertension like primary aldosteronism, Cushing syndrome, and hyperthyroidism.[31,32] Conflicting results have been reported for primary hyperparathyroidism.[31,33]

A nonexhaustive list of pathologies associated with nondipping BP profile is presented in Table 1. Most of these conditions are also associated with hypertension as mentioned above. Analysis of the pathophysiological mechanisms involved in these different conditions may lead to a better understanding of the mechanisms involved in the regulation of the circadian BP rhythm in essential hypertension.

Black ethnicity has been associated with reduced nocturnal BP fall and a higher rate of nondippers, which may contribute to the higher risk of target organ damage observed in African-Americans. South Asians have a higher stroke mortality rate but there is no proof in the literature of a higher rate of nondippers in that population.[34] It is also interesting to note that ambient temperature influences BP, which leads to seasonal BP variation. In summer, daytime BP is reduced, but not night-time BP, leading to a more common nondipping pattern than in winter.[35] Genetic factors are also related to the circadian BP variations and many other intrinsic cycles. A study performed on 260 patients has shown the heritability of dipping and the variability of BP and heart rate

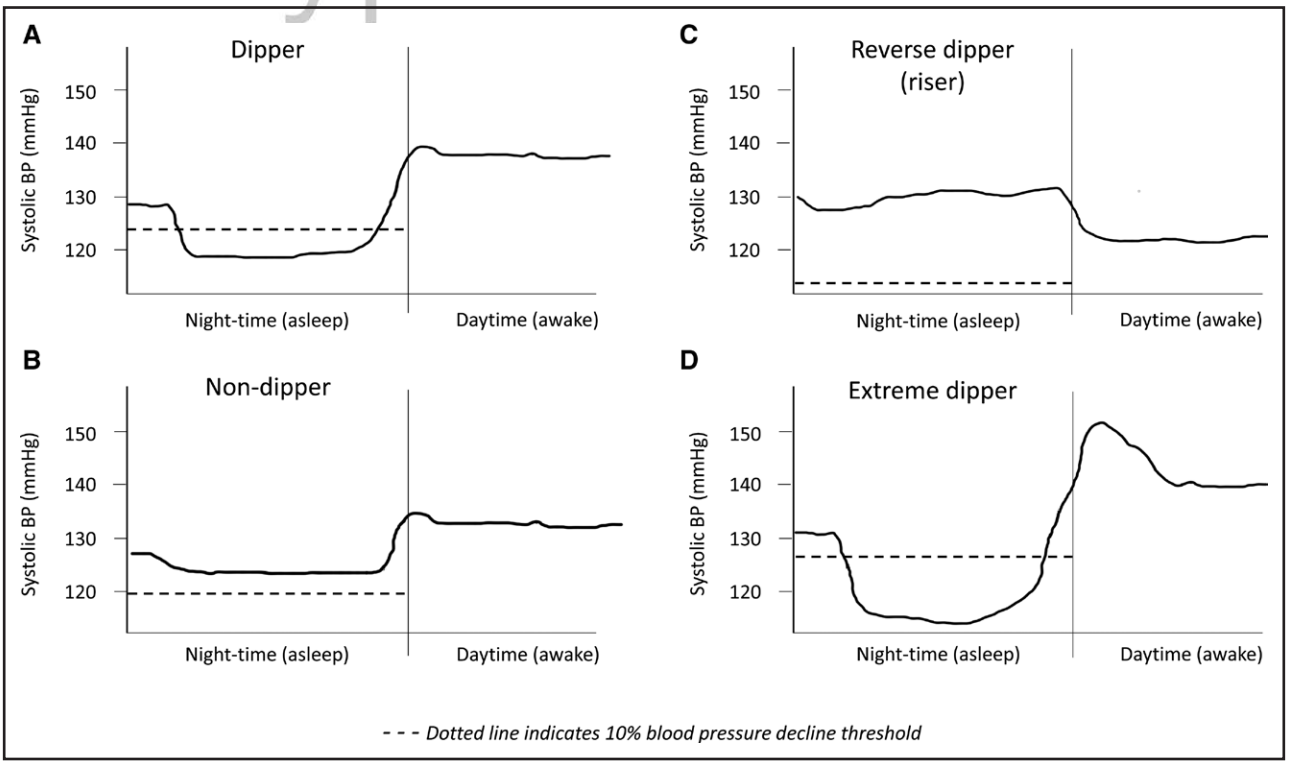

Figure 1. Illustration of the 4 patterns of diurnal blood pressure (BP) variation.
A, Normal dipping. **B**, Nondipping. **C**, Reverse dipping (rising). **D**, Extreme dipping with morning surge. Adapted from Cho et al[26].

Table 1. Nonexhaustive List of Pathological Conditions Associated With a Nondipping Blood Pressure Profile

Associated conditions
Endocrine conditions
Hyperthyroidism
Primary aldosteronism
Hyperparathyroidism
Hypercortisolism
Pheochromocytoma
Acromegaly
Renal dysfunction
Chronic kidney disease
Renal transplantation
Unilateral nephrectomy
Renovascular hypertension
Disturbances of the autonomic nervous system
Orthostatic hypotension
Diabetic neuropathy
Parkinson disease
Pure autonomic failure
Multiple system atrophy
Uremic neuropathy
Familial amyloidotic polyneuropathy
Sleep disturbances
Sleep deprivation
Insomnia
Obstructive sleep apnea syndrome
Restless legs syndrome
Narcolepsy
Other
Aging
Salt-sensitive hypertension
Ethnicity (African ancestry)
Seasonal variations
Pre-eclampsia
Malignant hypertension
Cardiac transplantation
Immunosuppressive therapy
Disturbances in circadian plasma melatonin levels
Genetic factors

Modified from Birkenhager et al[1]

at night.[36] Familial dysautonomia, for example is, a rare genetic condition, which could lead to nondipping.[37] A recent genome-wide association study involving 204 patients with essential hypertension showed an association between rs4905794 near *BCL11B* with nocturnal BP dipping but these data need to be replicated in an independent cohort.[38]

Short-acting antihypertensive drug therapy administered in a single morning dose may alter the diurnal BP pattern by inducing a greater reduction in BP during daytime than night time. BP during sleep is affected to a greater or lesser degree depending on the class of antihypertensive drug used (effect on BP during sleep in decreasing order: calcium antagonists, angiotensin-converting enzyme inhibitors, α [αβ] blockers, β blockers, and central adrenergic inhibitors).[39]

PATHOPHYSIOLOGY OF THE DIURNAL BP PROFILE

Circadian BP variation depends on the variation of hemodynamic parameters mostly related to 3 main factors: circadian rhythm, the autonomic nervous system, and water and sodium regulation.[1,40] Table 2 shows which of these factors are involved in pathologies associated with a nondipping BP profile. However, the precise mechanisms leading to a nondipping BP profile and the many interactions between them make things much more complex. The main interactions involved in the nondipping BP profile are illustrated in Figure 2.

Hemodynamic Parameters

A normal BP dipping pattern is mostly due to a decrease in cardiac output during the night, caused by a decrease in heart rate, while stroke volume remains generally stable compared to daytime. Night-time systemic vascular resistance does not change or may slightly increase. A nondipping BP pattern could therefore be due to a lesser nocturnal decline in cardiac output or to an exaggerated increase in systemic vascular resistance. A combination of both factors could also be present. Circadian changes in cardiac output and systemic vascular resistance are influenced by the sleep-activity cycle, including daytime changes in physical activity and posture, but also by several endogenous circadian rhythms that affect vascular and cardiac functions, notably by the autonomic nervous system, which regulates systemic vascular resistance and renin secretion, since the activity of the autonomic nervous system typically decreases during the night and is compensated by an increase in renin secretion to maintain BP (despite the fact that renin secretion is stimulated by the autonomic nervous system).[11,41–44]

Circadian Rhythm

The various mechanisms leading to a nondipping BP profile have recently been linked to altered molecular components of the circadian timing system.[11,16] The physiological circadian rhythm is controlled by a central clock located in the suprachiasmatic nucleus of the hypothalamus.[45] This nucleus acts via the autonomic nervous system, as well as via the pituitary and the pineal glands. The suprachiasmatic nucleus notably regulates the rhythmic production of melatonin by the pineal gland. Peripheral clocks located in the kidneys,

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Table 2. Main Mechanisms Involved in Pathologies Associated With a Nondipping Blood Pressure Profile

Main mechanisms involved in nondipping blood pressure profile	Associated conditions
Perturbations in sleep-activity cycle	Aging
	Sleep deprivation
	Insomnia
	Obstructive sleep apnea
	Chronic kidney disease
	Heart failure
	Restless legs syndrome
	Narcolepsy
Autonomic dysfunction	Aging
	Seasonal variations
	Orthostatic hypotension
	Obstructive sleep apnea
	Diabetes
	Chronic kidney disease
	Renovascular hypertension
	Hyperthyroidism
	Parkinson disease
	Renal or cardiac transplantation
	Hyperparathyroidism
	Quadriplegia
	Pure autonomic failure
	Multiple system atrophy
	Uremic neuropathy
	Familial amyloidotic polyneuropathy
	Pheochromocytoma
Water and sodium retention	Aging
	Seasonal variations
	High-salt intake
	Salt sensitivity
	Black ethnicity
	Heart failure
	Chronic kidney disease
	Renovascular hypertension
	Primary aldosteronism
	Hyperparathyroidism
	Hypercortisolism
	Autonomic failure
	Acromegaly

heart, and vessels are also involved.[45,46] Several pathologies have been linked to a circadian misalignment between peripheral and central clocks.[11,16,47] The circadian rhythm imposes rhythmicity on numerous biological functions over an ≈24-hour period and then needs to be entrained daily by Zeitgeber (time giver) signals, such as the light-dark cycle, in order to stay in synch with the environment.[48]

Focusing on the cardiovascular system, BP, heart rate, systemic vascular resistance, cardiac output, blood coagulation, and electrolyte excretion all follow distinct daily rhythms.[47] Melatonin, the major circadian hormone, has receptors present in the vessels of humans and animals,[49,50] and may thereby directly control blood flow.[46,51,52] The secretion of melatonin is increased during the night.[53] A study in a cohort of patients with hypertension showed a lower ratio of night/day concentration of melatonin in nondippers for DBP than in dippers, which suggests perturbations in the circadian rhythm of these patients.[46] Another study further supports this hypothesis, with the demonstration in nondippers of a deficit in the rhythmic excretion of melatonin metabolites in urine.[54] A significant and inverse association between the excretion of melatonin metabolites in urine during the night and the presence of a nondipping BP profile was reported in elderly hypertension patients.[55]

Several studies have investigated the impact of bedtime administration of melatonin on the night-time BP profile. Repeated melatonin administration before sleep has shown beneficial effects on BP in patients with essential hypertension, and also in adolescents with type 1 diabetes.[56,57] A more recent study performed involving a cohort of hypertension patients with type 2 diabetes has shown that 8 weeks of melatonin treatment restored a dipping BP profile (for systolic BP, diastolic BP, and MAP) in >30% of nondippers.[58]

Several other mechanisms of action that may link a disturbance in the circadian rhythm to a disturbance in the nocturnal BP profile have been suggested, with the identification of axes between the different circadian clocks. These axes are discussed in the Supplemental Material.

The sleep-activity cycle or the sleep-wake cycle is caused by the alternation of mutually inhibitory interactions between, on the one hand, hypnogenic and deactivating systems and, on the other hand, awakening and activating systems. Circadian oscillations of autonomic nervous system activity and renin secretion play an important role in the control of the sleep-wake cycle through interactions with the cardiovascular system.[11,59]

The behavior of an individual during the entire 24-hour period significantly impacts the normal circadian changes of the sleep-activity cycle by influencing these opposing systems, which in turn influences the BP circadian rhythm. Physical activity explains the largest proportion of these BP circadian variations.[60] A cycle of higher BP levels during daytime and lower BP levels during night-time most probably represents an anticipatory adaptation to higher demands during an active phase of a daily cycle.[47] Thus, an individual with a very intense day could become a dipper as the difference between his increased daytime BP and his night-time BP will be larger, which could explain why young people are dippers more frequently than old

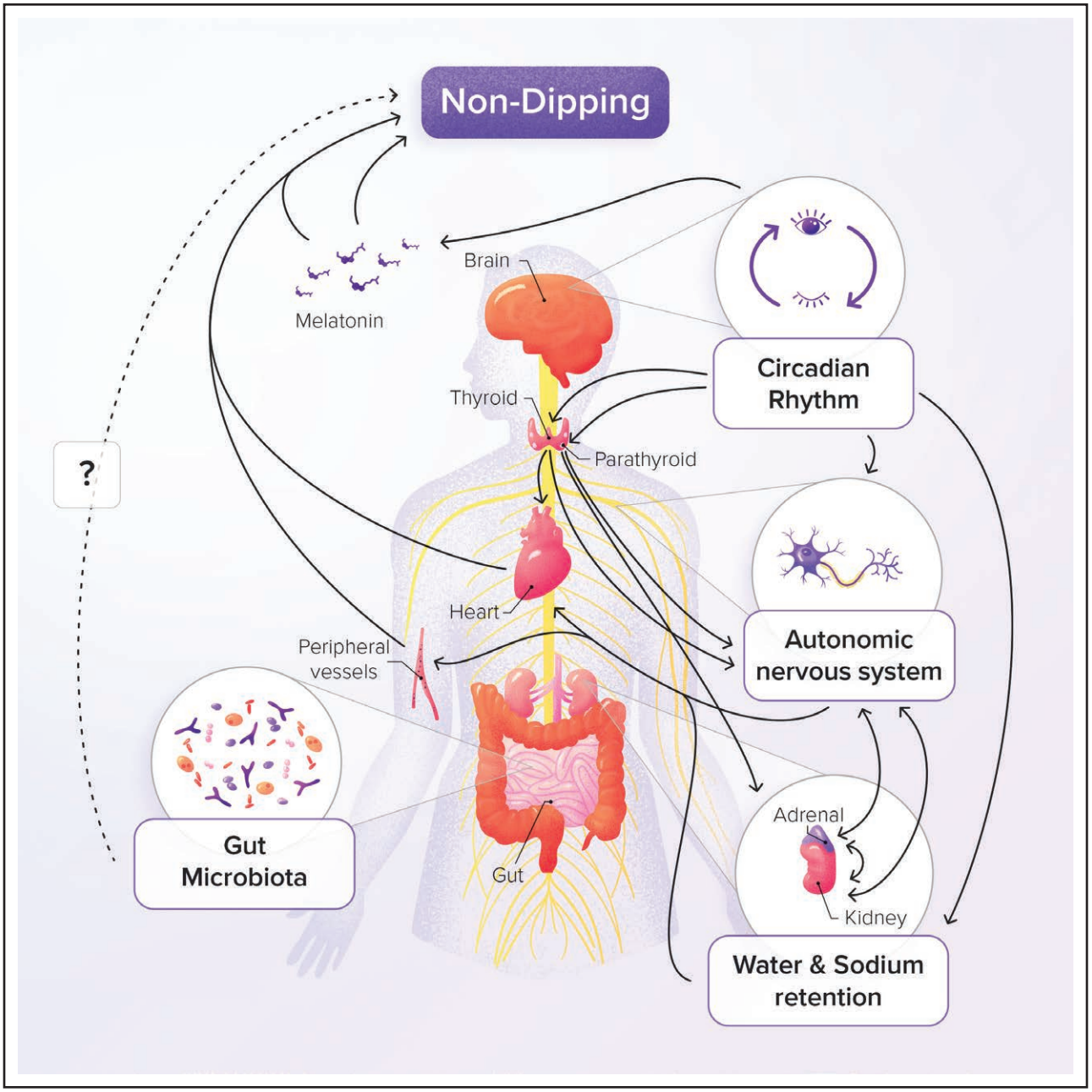

Figure 2. Outline of the complex interactions between main mechanisms leading to a nondipping blood pressure (BP) profile.

people.[1] A study comparing the night-time BP profile in 43 patients has reinforced this hypothesis by showing that more patients were categorized as nondippers when the ambulatory blood pressure monitoring was performed in a less active day.[41,61]

Similarly, periods of wakefulness and sleep considerably impact BP.[1,62,63] The different sleep stages differentially influence the cardiovascular system. BP dipping occurs during nonrapid eye movement sleep because of parasympathetic predominance during this sleep stage.[26] Deepest sleep stages are associated with lowest BP levels, while less deep sleep stages are associated with higher BP levels, but still lower than awake-time levels.[64] By contrast, during rapid eye movement sleep (which is more present during the second part of the night), sympathetic activity increases significantly in a highly variable way, causing variable night-time BP, which may reach awake-time BP levels. This has been demonstrated indirectly by catecholamines measurement and directly by microneurography.[26,64,65] Heart rate and systemic vascular resistance are also modified according to these changes in the autonomic nervous system. Finally, brief episodes of awakening induce an increase in night-time BP.[64] Microarousals during sleep are significantly more frequent in nondippers than in dippers with essential hypertension and are associated with

increased heart rate and BP.[66] Declining renin secretion coincides with rapid eye movement sleep phases, while increasing levels of renin are detected in nonrapid eye movement sleep phases.[67] Nocturnal BP is thus tightly regulated by the different sleep architecture and patterns. Hence, any perturbation in sleep quality or quantity may lead to the development of the BP nondipping pattern (Table 2) by worsening night-time hypertension. Note that sleep disturbances have also been associated with metabolic syndrome, obesity, and glucose metabolism disorder.[26]

Moreover, the nondipping BP pattern has been correlated to the apnea-hypopnea index used to grade obstructive sleep apnea syndrome (OSAS), a pathological condition inducing significant sleep disturbances and increased sympathetic activity in response to episodes of hypoxia during sleep. OSAS is frequently associated with nondipper or riser BP profile.[68–72]

According to the cause of nocturnal hypertension, supportive or active strategies to improve the quality or quantity of sleep may be required, for example psychological consultation, proper management of neurological diseases, or the use of a continuous positive airway pressure device in OSAS.[26] However, OSAS causes modifications in BP variability, which are not corrected by continuous positive airway pressure.[63]

The Autonomic Nervous System

The final common pathway in the regulation of BP circadian rhythm is the autonomic nervous system.[11,73–75] A good illustration of the fact that central sympathetic control is essential for normal BP circadian changes is the loss of BP circadian variations in patients with quadriplegia due to cervical spinal cord injuries, while BP circadian rhythm is preserved in patients with paraplegia due to thoracic spinal cord injuries.[76,77] The regulation of the renin-angiotensin-aldosterone system is also, at least in part, mediated by the activation of the autonomic nervous system.[69,78,79] Therefore, it is not surprising that autonomic dysfunction is strongly associated with nondipping BP profile and nocturnal hypertension. Table 2 shows examples of pathologies leading to autonomic nervous system dysfunction.

Patients with dysautonomia (ie, multiple system atrophy, pure autonomic failure, or Parkinson disease) may experience impressive postural BP changes, with a considerable drop in their BP when standing and a rise in BP when lying down, leading to riser profile.[80] Inadequate preload reserve, insufficient arterial resistance, and abnormal cardiac performance have been postulated to contribute to orthostatic hypotension observed in these conditions.[81] Supine hypertension may be at least in part due to mobilization through the whole body of the pooled blood accumulated in the legs when patients are standing during the day, which leads to an increase in cardiac output (by increasing stroke volume) and then an increase in supine BP.[1] Hypercontractile left ventricular performance has been found in patients with dysautonomia and has been correlated with increased peripheral arterial resistance when patients are lying down.[81] However, depending on the pathology considered, the pathophysiological mechanism may vary.[80] Supine hypertension is fully driven by residual sympathetic activity in multiple system atrophy while this is only partially the case for supine hypertension in pure autonomic failure.[82]

OSAS, pheochromocytoma, renovascular hypertension, and primary hyperparathyroidism (through hypercalcemia) are other examples of pathologies involving an autonomic nervous system dysfunction that lead to a nondipping BP profile. In these pathologies, high sympathetic tone or increased concentrations of circulating catecholamines are responsible for a pathological increase in nocturnal BP through an increase in vascular tone.[1,33,83,84] Nondipping has also been observed more frequently in cardiac transplant recipients, which is probably related to the denervated state of the transplanted heart.[85] Finally, a decrease in norepinephrine secretion leading to daytime vasodilatation has been identified as the cause of lower daytime BP levels and a higher rate of nondipping when ambient temperature is higher in summer.[35]

Some strategies have been proposed to decrease nocturnal BP through modulation of the autonomic nervous system when a sympathetic overdrive is present. For example, one study has showed a significant improvement in nocturnal BP when α-blocker doxazosin was administered in the evening.[86] Renal denervation, which has been proposed in the treatment of refractory hypertension, has also been shown to induce a significant reduction in nocturnal BP.[26,87] Several new strategies to modulate the autonomic nervous system, such as baroreflex activation, are still under investigation.[41] For patients with dysautonomia and supine hypertension, sleeping with the head of the bed elevated is advised. The use of short-acting antihypertensive drugs at bedtime may also be considered. However, their efficacy with regard to nocturnal BP is limited and caution is needed because they may increase the risk of a fall during the day.[1,88]

Water and Sodium Regulation

Salt excess and volume overload have been involved in the nondipping BP profile. Salt-sensitive hypertension patients are more frequently nondippers[89] and excess sodium intake in subjects with normal renal function is probably one of the main factors causing nondipping in essential hypertension.[90] Water and sodium homeostasis are partly regulated by the renin-angiotensin-aldosterone system, and as discussed above, the renin-angiotensin-aldosterone system plays an

important role in BP circadian rhythm via its connections to the autonomic nervous system.[11] Renin secretion is increased during sleep and 24-hour plasma renin activity variations have been shown to be related to sleep processes.[59]

Pressure-natriuresis is one of the main physiological mechanisms involved in the maintenance of sodium balance. Sodium excretion is normally lowest at night as BP decreases. In patients presenting with sodium retention, BP increases, leading to protracted sodium excretion during the night, which can result in a nondipping BP profile. It has been shown that the circadian rhythm of renal sodium excretion differed between dippers and nondippers with essential hypertension.[11,89,91]

One of the proposed mechanisms to explain nondipping in salt-sensitive hypertension patients is an impaired baroreflex function causing a sympathetic activation, since short-term exposure to a high-salt diet in normotensive patients leads to a decrease in the carotid baroreceptor reflex function.[92] In an animal model, salt sensitivity has been linked to endothelial dysfunction, since high-salt diet increased nitric oxide activity in salt-resistant rats only and not in salt-sensitive rats. A decrease in nitric oxide release has been found in nondippers, which leads to a blunted endothelium-dependent vasodilation.[69,93,94]

Numerous pathological conditions associated with the nondipping BP profile are at least in part related to water and sodium retention: it is notably the case for hypercortisolism, primary aldosteronism, hyperparathyroidism, acromegaly, autonomic failure, renovascular hypertension, and chronic kidney disease (Table 2). The precise mechanisms involved in these pathologies are discussed in the Supplemental Material.

The higher prevalence of a nondipping BP pattern found in African-Americans has also been linked with higher salt sensitivity, as well as with more frequent hypertensive renal damage in this population.[34,95,96] Along the same lines, the seasonal variation in dipping status has also been linked to a decrease in transpiration and in PTH secretion due to lower ambient temperature during winter with higher water and sodium retention leading to increased BP levels during daytime.[35]

Several therapeutic strategies that counteract water and sodium retention have shown good results in the treatment of nondipping BP profile. Lifestyle modifications focusing on salt restriction help to reduce nocturnal BP levels only in salt-sensitive patients. Thiazide

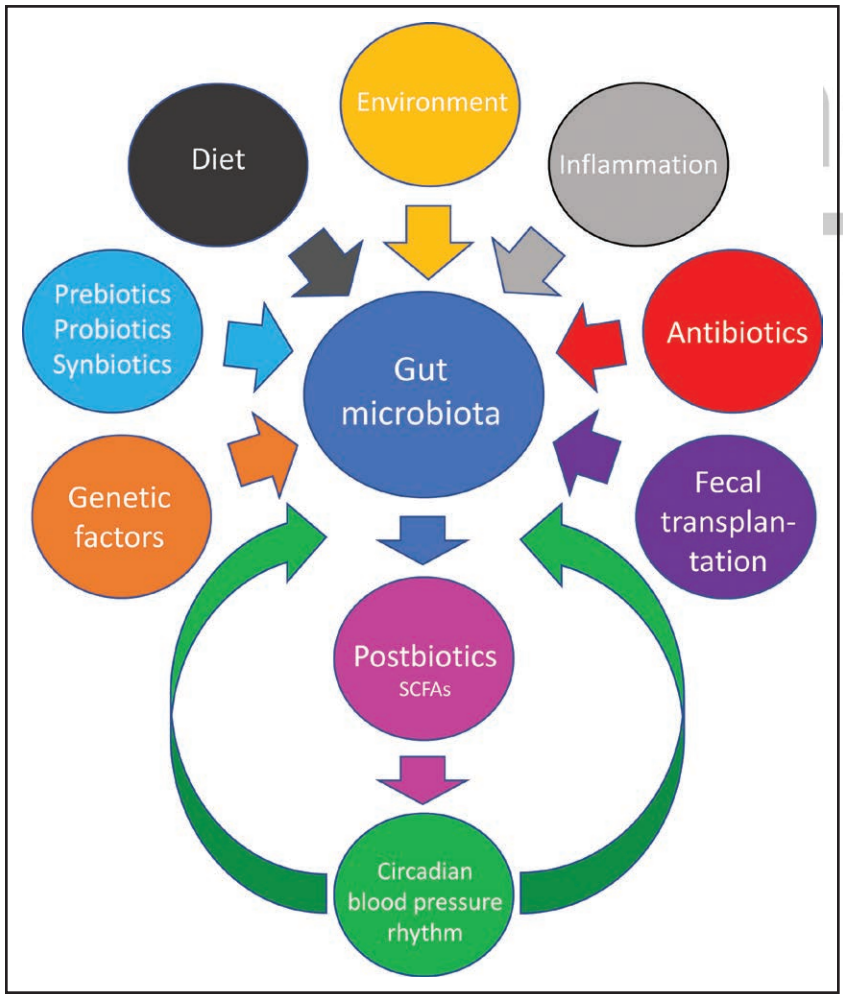

Figure 3. Hypothetic role of gut microbiota and SCFAs in the circadian blood pressure (BP) rhythm.
SCFAs indicates short chain fatty acids.

diuretics may help to improve the dipping profile by inducing natriuresis.[91,97–99]

Role of Dysbiosis and Metabolites Derived From Gut Microbiota in BP Dipping

Alterations in the composition of gut microbiota, also called dysbiosis, are caused by various endogenous and exogenous factors. Gut microbiota has been involved in the pathophysiology of various pathologies, such as diabetes, inflammatory bowel disease, obesity, liver diseases, chronic kidney disease. and hypertension in numerous preclinical and clinical models.[100–109] Correlations between fecal bacterial taxa (eg, g_*Sutterella*) and BP dipping was found in a recent study in Dahl salt-sensitive rats.[110] Further reports, including studies in humans, are needed to confirm this putative link between gut microbiota composition and the diurnal BP profile.

The implication of gut microbiota-derived metabolites (also called postbiotics), like the short chain fatty acids, in several pathologies including BP homeostasis is becoming increasingly recognized.[104,111–116] Two recent studies in nondippers and dippers patients have shown a good discrimination between both groups based on stool metabolome,[28] with higher amounts of the 3 main short chain fatty acids (ie, acetate, propionate, and butyrate) in the stools of nondippers compared with dippers in both men and women.[28,117] This pathophysiological hypothesis is presented in Figure 3 and more details are given in the Supplemental Material.

THERAPEUTIC MANAGEMENT

Some specific therapeutic strategies have already been discussed above, such as treatment of sleep disorders including OSAS, treatment of supine hypertension in patients with dysautonomia, treatment of neurological and endocrine disorders, sodium restriction, thiazide diuretics and melatonin administration at bedtime. Table S1 also shows specific treatments for different conditions associated with nondipping.

Except in specific situations like supine hypertension associated with orthostatic hypotension, long-acting antihypertensive drugs should be preferred to control BP throughout the entire 24-hour period. They also have the advantage of increased adherence since there is only one administration per day. The concept of chronotherapy consists in administering a medication preferentially at bed-time rather than at wake-up, which may (1) increase the efficacy of antihypertensive drugs on nocturnal BP, (2) restore the circadian variation of BP, and (3) correct the blunted nocturnal BP decline in nondippers. However, chronotherapy is not endorsed by the European Society of Hypertension guidelines following methodological issues and doubts about the published outcome studies,[118,119] which have been seriously questioned by most scientists.[120–122] Molecules other than classical antihypertensive drugs have shown an efficacy in reducing night-time BP, as seems to be the case for melatonin treatment (as seen above[58]) and for mineralocorticoid receptor antagonist spironolactone (which is effective in resistant hypertension [123]). The impact of SGLT2 (sodium-glucose cotransporter-2) inhibitors on nocturnal BP levels still needs to be clarified.[124]

CONCLUSIONS

A nondipping BP profile confers a high cardiovascular and renal risk. Its presence must therefore be carefully checked by several 24-hour BP recordings. Its pathophysiology is complex. Nondipping is frequently present in secondary hypertension and analysis of the mechanisms involved in these different conditions may lead to a better understanding of circadian BP variations in essential hypertension. All the mechanisms explained above are most probably involved in nondippers with essential hypertension in a more or less significant way, particularly salt overload. Further translational research is required to (1) improve our understanding of BP dipping pattern, (2) identify the best strategies to restore a normal BP profile, and (3) prevent its associated adverse prognosis.

ARTICLE INFORMATION

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Supplemental Material

Table S1

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