Nocturnal Sodium Excretion, Blood Pressure Dipping, and Sodium Sensitivity

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More than 30 years ago, Guyton described pressure-natriuresis: increasing arterial blood pressure promotes sodium excretion, decreasing blood volume and lowering blood pressure, whereas when blood pressure falls, sodium excretion decreases, and blood volume and blood pressure increase. The linchpin of the model of Guyton et al. is the concept of feedback gain. Gain is the degree to which a feedback system can correct a perturbation, that is, the amount of correction of a deviation divided by the residual degree of deviation. When a control system corrects a perturbation minimally, its feedback gain is near 0. When it corrects it completely, its gain is infinite. As emphasized by Guyton et al., in integrated systems with infinite and finite gain components, the infinite gain function ultimately dominates. There are myriad blood pressure control systems, for example, arterial baroreceptors and chemoreceptors, the central nervous system ischemic response, the renin-angiotensin system, and capillary fluid shift, but all are ultimately trumped by pressure-natriuresis. In the experiments by Guyton et al., pressure-natriuresis had near infinite gain over a wide range of urinary sodium excretion, such that the set point of blood pressure regulation was not affected by sodium intake over a period of several days or a few weeks.

This pressure-natriuresis model describes a steady-state relationship. At short time intervals, blood pressure and sodium excretion may not be closely linked, but the body will always eventually bring the system back into balance. In this review, we wish to draw attention to differences in the relationship of blood pressure to sodium excretion during day and night and to how nighttime pressure-natriuresis and sodium sensitivity of blood pressure interact. We will suggest that these features of pressure-natriuresis have implications both for the clinical management of hypertension and research into the genetic underpinnings of the disease.

Diurnal Rhythm of Sodium Excretion in Normotensive and Hypertensive Subjects

In healthy people, sodium excretion reaches a maximum during the day and a minimum at night during sleep, and it has long been thought that blood pressure is the primary determinant of nighttime sodium excretion. Centonza et al. performed ambulatory blood pressure monitoring over a 26-hour period in normotensive subjects for whom sodium intake was fixed at a moderate amount (170 mmol/day). All of the subjects demonstrated a nocturnal dip in blood pressure with a concomitant dip in sodium excretion. Moreover, there were significant positive correlations between blood pressure and sodium excretion during the night and over 24 hours, as well as during periods of quiet supine wakefulness and postprandial sitting. No similar relationship was apparent when subjects carried out daily activities in the standing position. The authors concluded that the pressure-natriuresis relationship is blunted during upright posture, possibly because of the activation of neurohumoral systems. Staessen et al. also observed that both systolic and diastolic blood pressure correlate with sodium excretion only during sleep. Staessen et al. went on to show that office systolic and diastolic blood pressures also correlated positively with nighttime sodium excretion, and Dyer et al. found the same relationship using a night/day sodium excretion ratio. Taken together, these studies strongly suggest that the pressure natriuresis relationship, although always active, is most clearly revealed when least confounded by the effects of circulating hormones, for example, angiotensin and aldosterone, and sympathetic nerve activity.

Hypertensive subjects have higher nighttime sodium excretion rates than normotensive subjects. Dyer et al. measured office blood pressure and overnight and 24-hour urinary sodium excretion in 107 hypertensive men and women and observed that more than half exhibited a greater rate of sodium excretion when asleep than during the day. When compared with 30 people with high-normal blood pressure, hypertensive subjects had significantly higher night/day sodium excretion ratios. The group also conducted a small meta-analysis, which confirmed that night/day ratios of sodium excretion were higher in hypertensive subjects compared with those of normotensive and borderline hypertensive subjects. Wide variation of subject age, however, might have confounded this analysis, because older subjects tend to have higher ratios than younger subjects.

Bultasova et al. supported the findings of Dyer et al. in a small study comparing circadian rhythms of sodium excretion in 8 young borderline hypertensive men and 6 healthy age-matched normotensive subjects. All of the subjects maintained normal daily activities, but nighttime studies were...
performed in hospital after adaptation to a regimen of sleep between 10:00 PM and 6:00 AM and to a 135-mmol sodium per day diet. In borderline hypertensive subjects, the curve of sodium excretion was flat, and a higher proportion of sodium was excreted at night. Normotensive subjects had the expected nocturnal decrease in sodium excretion.

Kawano et al\textsuperscript{15} presented a contrasting result. Their study of 20 normotensive, 20 borderline hypertensive, and 10 mildly hypertensive middle-aged men found that all of the groups had a normal pattern of high sodium excretion during the day and low output at night. Nighttime blood pressure was not measured in this study, and it is, therefore, not possible to compare the pressure-natriuresis relationship in this study with those above. For the most part, these relatively small investigations demonstrate that hypertensive subjects have a blunted circadian pattern of sodium excretion compared with normotensive subjects, with a greater fraction of daily sodium output occurring at night.

**Nocturnal Blood Pressure Dipping and Sodium Excretion**

Diurnal variation in blood pressure has been investigated extensively since the advent of automated blood pressure monitoring, and various patterns have been distinguished: individuals whose blood pressure falls normally at night are “dippers,” whereas those in whom it does not are “nondippers” (and there is “reverse dipping,” about which we will not be further concerned).\textsuperscript{16–18} Although there is no standard definition, a fall of mean arterial pressure (MAP) by >10% from day to night is heuristically useful. Nondipping is more than a physiological curiosity, because nondippers are reported to experience more serious target-organ damage, including left ventricular hypertrophy, microalbuminuria, and cerebrovascular disease, than dippers.\textsuperscript{16–22} As noted, sodium excretion also normally declines at night, but in some it does not: there does not seem to be a term analogous to “nondipper” for individuals whose nocturnal sodium excretion does not fall at night.

Because higher nighttime blood pressure is associated with greater sodium excretion, dippers and nondippers should have different circadian rhythms of sodium output. Fujii et al\textsuperscript{23} addressed this issue in a study of essential hypertensive subjects maintained on high- or low-sodium diets, each for 1 week. Eight patients were classified as dippers based on a fall in MAP of >10% from day to night on the high-sodium diet; the rest were nondippers. During the high-sodium diet, the night/day ratio of sodium excretion rate was <1 in dippers, whereas in nondippers it was >1, that is, nocturnal sodium excretion did not decline. After adaptation to the low-sodium diet, the ratio of night/day sodium excretion decreased to <1 in the nondippers, not significantly different from that of dippers. Thus, low-sodium intake restored a normal night/day sodium excretion pattern. In all of the subjects, regardless of dipping status, the night/day ratio of sodium excretion correlated with that of MAP on the high- but not the low-sodium diet.

In a related study, the same group investigated whether upright postural change decreased the rate of sodium excretion.\textsuperscript{24} Subjects adhered to a protocol identical to the aforementioned one, except that on day 7 of the high-sodium diet, they were upright from 8:00 AM to 10:00 AM and supine from 10:00 AM to 12:00 PM. Findings from the previous study regarding the relationship of nocturnal blood pressure and sodium excretion were replicated. Sodium excretion was significantly lower during standing in nocturnal blood pressure nondippers than in dippers, and there was an inverse relationship between the upright/supine ratio and the night/day ratios of both MAP and sodium excretion. Thus, nondippers behave as if they retain sodium during the day, perhaps because of vigorous antinatriuresis during upright activity, and excrete the excess sodium at night. Over the 24-hour period, sodium intake and output are balanced.

Nondipping is common in 2 diseases that compromise renal sodium excretion, chronic renal insufficiency and congestive heart failure (CHF). Indeed, in renal disease, nondipping is the rule, with a prevalence between 74% and 82%.\textsuperscript{25–29} Cross-sectional observations have demonstrated that nondippers have more severe morphological\textsuperscript{30} and functional\textsuperscript{31,32} changes than dippers. Fukuda et al\textsuperscript{31} studied subjects with biopsy-proven glomerulopathy and found that creatinine clearance (ClCr) was significantly negatively related to the night/day ratios of both sodium excretion and MAP, whereas Farmer et al\textsuperscript{32} have shown that the prevalence of nondipping increases with plasma creatinine concentration in patients with chronic renal insufficiency. In addition, prospective studies show that nocturnal blood pressure is closely related to the progression of renal damage. Lurbe et al\textsuperscript{33} observed that nondipping progressed in type 1 diabetics who developed microalbuminuria but not in those who maintained normal albumin excretion. Furthermore, in that study, an increase in blood pressure during sleep preceded the development of microalbuminuria, as well as rises in office and daytime ambulatory blood pressure. Perrin et al\textsuperscript{30} found that both nondipping and the renal morphological changes of type 1 diabetic nephropathy progressed over 6 years and that nighttime systolic and MAP are strong predictors of pathology.\textsuperscript{34} Finally, it has also been reported, although not universally, that a circadian rhythm of blood pressure is restored by kidney transplantation.\textsuperscript{32,35}

Patients with CHF, a prerenal cause of sodium retention, may also be nondippers,\textsuperscript{36,37} although this has not been observed universally.\textsuperscript{38} Nondipping seems to worsen as left ventricular function deteriorates, as reported by both Caruana et al\textsuperscript{39} and Van de Borne et al.\textsuperscript{40} Furthermore, the improvement of systemic hemodynamics resulting from treatment of CHF with angiotensin-converting enzyme inhibitors, regardless of the effect on 24-hour MAP, increases the circadian variation of BP.\textsuperscript{41} No one has yet related dipping status to the circadian rhythm of natriuresis in CHF.

Nondipping of blood pressure seems to be associated with increased nocturnal sodium excretion. The most parsimonious explanation of the association is that sodium retention during the day must be compensated for at night to maintain long-term sodium balance.

**Dipping and Sodium Sensitivity of Blood Pressure**

Traditionally, individuals whose blood pressure varies with changes in sodium intake are termed “sodium sensitive” (SS),
whereas those whose blood pressure does not are “sodium resistant” (SR). It should be noted, however, that this dichotomous classification is misleading, because populational responses are continuously distributed, and definitions of SS and SR, therefore, are arbitrary. For example, some define sodium sensitivity as a 10% increase in MAP with a sodium load, whereas others have suggested that increases of 8, 5, or 3 mm Hg are sufficient. Also, to what degree sodium is restricted and supplemented and for how long varies, as does the method of sodium manipulation, for example, dietary or acute volume loading and depletion. Nonetheless, the general principle that blood pressure responds to dietary sodium intake in some individuals has been well supported, and the prevalence of sodium sensitivity has been found to be higher in hypertensive than normotensive subjects, blacks than whites, and elderly than young.42

Uzu et al investigated the relationship between sodium sensitivity and diurnal variation of blood pressure in essential hypertension. Twenty-eight hypertensive subjects were maintained on high- or low-sodium diets for 1 week each in a controlled setting. Sodium sensitivity was defined as a fall of ≥10% in average 24-hour MAP with sodium restriction. In the SR group, MAP dipped during the night on both high- and low-sodium diets. In the SS group, on the other hand, there was no nocturnal fall in MAP on either diet. The authors concluded that SS patients with essential hypertension are likely to manifest as nondippers.

Although, as noted, sodium sensitivity is almost always presented as a categorical phenotype, it can also be characterized as a continuous measure. Uzu et al calculated a sodium sensitivity index (SSI) as the ratio of the change in 24-hour MAP divided by the change in sodium excretion on high- and low-sodium diets in steady state. During high sodium intake, SSI correlated significantly with nighttime MAP, but a similar relationship was not observed during the low-sodium diet. In addition, in a subsequent study by Uzu et al., 18 subjects were significant difference between the means, regardless of the magnitude of the change. By this definition, 18 subjects were SS and 22 were SR. This novel definition of sodium sensitivity could explain the results, at least in part: only 6 subjects would have been classified as SS using the more widely accepted definition of a 10% change of MAP. Thus, it is difficult to afford much weight to this investigation given the consistency of the relationship between nondipping and sodium sensitivity in the studies reviewed previously.

Sodium sensitivity and nondipping are also both found in patients with primary aldosteronism. In addition, both Uzu et al. and Takakuwa et al. showed that dietary sodium restriction restores the nocturnal dip in blood pressure in patients with primary aldosteronism.

Diuretics reproduce the effect of dietary restriction on sodium balance, and Uzu and Kimura49 reported that 4 weeks of treatment with 25 mg of hydrochlorothiazide converted 11 nondipping hypertensive subjects to dippers. In a randomized, placebo-controlled comparison, antihypertensive responses to 12 weeks of hydrochlorothiazide treatment were significant in nondippers but not in dippers.51 Effects of other drug classes on dipping have been reviewed recently.52

We conclude that although there is not complete consensus, there seems to be a strong concordance between sodium sensitivity and nondipping in hypertensive subjects. We suggest that there are different limits to sodium excretory capacity between individuals, which are revealed when sodium intake increases. SS individuals respond to sodium loading as if their daytime capacity is insufficient to maintain sodium balance so that they must excrete a greater proportion of sodium at night to maintain overall sodium balance. Nocturnal sodium excretion is affected by adjusting blood pressure upward to stimulate pressure–natriuresis, resulting in nondipping. During sodium restriction or after diuretic treatment, sodium excretory requirements fall back with the range that can be met by daytime excretion, eliminating the need for high blood pressure at night and restoring a dipping pattern.

What Renal Mechanisms Regulate Nocturnal Sodium Excretion?

Although we have emphasized the primacy of pressure–natriuresis in the control of nocturnal sodium excretion, kidneys are not passive conduits through which blood pressure drives sodium toward the urine. Indeed, the myriad adjustments, both intrinsic to and outside of the kidney, as well as their complex, highly integrated interactions, are the focus of the systems analysis approach championed by Guyton et al. (and presently elaborated in a computer simulation available from the Department of Physiology and Biophysics of the University of Mississippi Medical Center [http://physiology. umc.edu]).

Dipping and Renal Hemodynamics

The relationship of dipping to glomerular filtration rate and renal hemodynamics in essential hypertensive subjects with globally normal renal function is largely unstudied. To our
knowledge, the only investigation that has assessed glomerular function in dippers and nondippers described only modest differences. Fuji et al. reported that creatinine excretion rate (milligrams per hour) increased from day to night in nondippers on a high-sodium diet (48±19 to 51±22 mg/h) but decreased during a low-sodium diet (49±20 to 45±21 mg/h). In dippers, creatinine excretion rate decreased from day to night on both high- and low-sodium diets (64±28 to 56±40 mg/h) on high sodium (58±15 to 46±13 mg/h on low sodium). Because serum creatinine concentration is unchanged over the course of 24 hours, differences in creatinine excretion result from differences in ClCr. Changes in ClCr in nondippers, therefore, seem to parallel changes in natriuresis.

In the absence of direct investigation, further insights into the renal physiology of dipping rest on the concordance of nondipping and sodium sensitivity suggested above. Although recognizing that the 2 conditions are not always found together, observations in sodium sensitivity may suggest useful avenues for further studies of dipping and nocturnal sodium excretion.

There is agreement that in response to sodium loading SR subjects dilate their renal vasculature, whereas SS individuals do not: vasodilatation seems to be an important part of the natriuretic repertoire of the kidney. Ando and Fujita characterized differences in ClCr and renal blood flow (RBF) determined by clearance of 125Iodine para-amino hippurate) in 6 SS and 14 SR hypertensive subjects in low- and high-sodium diets. ClCr did not differ between the 2 groups while on a high-sodium diet, but renal vascular resistance (RVR) was greater in the SS subjects, and responses of RVR and MAP to sodium loading were significantly correlated. Schmidlin et al. demonstrated in SS hypertensive subjects that a 3-week sodium load lowered RBF, increased RVR, and increased filtration fraction from 19.4% to 21.4% (P<0.001). SR hypertensive subjects showed no significant changes. Campese et al. confirmed that RBF decreases in response to a sodium load only in SS hypertensive subjects. In that study, glomerular filtration rate did not change in either SS or SR hypertensive subjects, and, accordingly, filtration fraction increased in the SS group. Williams and Hollenberg have used responses of RBF to distinguish subgroups of “modulating” and “nonmodulating” normal renin hypertensive subjects. Compared with modulators, that is, those who decrease RBF during angiotensin II infusion and tend to be SR, nonmodulators have blunted responses to angiotensin II and are more SS. Although not reviewed here, observations in a number of animal models of sodium sensitivity parallel those in humans, although which (if any) models of human pathophysiology of sodium sensitivity are unknown.

**Segmental Renal Tubular Sodium Transport**

Regulation of renal sodium excretion is effected by the activity of renal tubular transporters and channels. In humans, these pathways adjust sodium excretion can be partially characterized using noninvasive clearance methodologies to quantify sodium reabsorption in renal tubular segments. We are not aware of any reports of how segmental tubular transport is related to nocturnal sodium handling or how it may differ between dippers and nondippers.

Once again, it is possible that clues to the patterns of nocturnal blood pressure and sodium excretion may be found in sodium sensitivity. Burnier et al. using the endogenous renal lithium clearance (ClLi) method, a well-validated measure of total proximal tubular sodium reabsorption, found that SS subjects do not suppress proximal sodium reabsorption as effectively as SR ones in response to sodium loading. ClLi measurements do not permit distinction between the several mechanisms mediating proximal tubular sodium reabsorption, but the finding is consistent with the renal hemodynamic studies reviewed above: the increase in filtration fraction observed in SS hypertensive subjects should increase peritubular oncotic pressure and promote sodium reabsorption in the proximal tubule.

Thick ascending loop of Henle (TAL) function is less accessible to measurement in humans than that of the proximal or distal tubules, but Aviv et al. have presented a plausible model in which enhanced TAL sodium chloride cotransport could promote sodium sensitivity of blood pressure. As yet, there are no studies comparing dippers and nondippers for measures of TAL activity, which, in humans, are at present limited to measurements of maximal diluting and concentrating ability.

The distal tubule is the final arbiter of sodium balance and, therefore, a potentially key site contributing to sodium sensitivity. Distal tubular sodium delivery and reabsorption can be calculated from measurements of ClLi and total sodium excretion, but to our knowledge such measurements have not been performed to compare dippers and nondippers. However, it seems quite likely that distal tubular mechanisms are important. As noted above, increased distal tubular sodium reabsorption in the hypertension of primary aldosteronism, the classic example of sodium sensitivity, is a clear illustration of the relationship of sodium sensitivity and nondipping. The restoration of dipping in SS hypertensive subjects by hydrochlorothiazide treatment suggests that less dramatic increases in distal tubular sodium reabsorption than those of aldosteronism are also important and that other distally acting diuretics (aldosterone antagonists and epithelial sodium channel blockers) should also affect dipping. Because of their pharmacodynamic specificities, these agents may also help in characterizing the activity of individual distal tubular sodium transport pathways, as in the study by Pratt et al., which used amiloride as a probe of epithelial sodium channel activity. Other approaches involving measurements of renal tubular transporter activity in other cells, including circumferential blood cells and the oral mucosa, may also have promise.

**Conclusions**

Dynamic, flexible regulation of renal sodium excretion is needed to respond to variations, both short and long term, in sodium intake. Of the physiological mechanisms invoked to maintain sodium balance, pressure–natriuresis is preeminent. Because blood pressure is normally lowest at night, sodium excretion is as well, but if sodium has been retained during the day, blood pressure is adjusted to the higher level needed to eliminate it, and nondipping results. It is, therefore, not
surprising that those hypertensive subjects prone to retain sodium to a degree that affects blood pressure, that is, SS individuals, are generally nondippers. The pressure–natriuresis relationship, obscured during the day by the effects of upright posture and activity but released at night to function unfettered, underlies both nondipping and sodium sensitivity.

Based on these considerations, optimizing antihypertensive therapy (pharmacological or dietary) could include attention to restoration of normal circadian variation in blood pressure and sodium excretion. Efficacies of the various classes of antihypertensive drugs for restoring normal dipping are not well studied, but it seems that diuretics, angiotensin-converting enzyme inhibitors, and angiotensin-I receptor blockers and calcium channel blockers (amlodipine and nisoldipine) are somewhat helpful, whereas \( \alpha \)- and \( \beta \)-blockers are less so (reviewed in Reference 52). In addition to drug mechanism, the timing of dosing can be used to advantage; a modification as simple as switching the dosing of an angiotensin-I receptor blocker from morning to evening may be all that is needed.\(^6\) Dietary potassium supplementation and sodium restriction also restore normal dipping, and such interventions could enhance the effect of drug therapy on nighttime blood pressure.\(^6\)

In addition to serving as a guide to optimizing therapy, characterizing nocturnal sodium excretion patterns and control mechanisms may lead to a better understanding of subtypes of "essential" hypertension. For instance, hypertensive subjects who excrete less sodium at night may have a different underlying pathophysiology than those who excrete normal amounts. RBF measurements could reveal "vasodilator" and "vasoconstrictor" subtypes affecting nocturnal pressure–natriuresis. It is our opinion that characterization of renal tubular transport functions, for example, with \( \mathrm{Cl}_\mathrm{i} \) measurements, is particularly promising: perhaps there are "proximal" and "distal" subtypes of hypertension differing in pathophysiology and requiring tailored therapeutic approaches.

Finally, we wish to close with a further homage to Guyton and an extension of his approach to the era of human genomics. Guyton was an early advocate of the systems approach, because he recognized a fundamental truth of biological research, that complex systems are characterized by emergent properties, and, as a consequence, isolated organ, tissue, cellular, or genomic systems cannot, even theoretically, predict responses at higher physiological levels. It is indeed true that the whole is more than the sum of its parts, and clinical research should begin with that whole.

It is equally true that the proper study of humans is humans. Hypertension research, particularly that related to genetics, has been dominated by studies of inbred rat strains, which were developed by truncating selection for the phenotype of hypertension. It beggars the imagination to believe that artificial selection could have fixed alleles of genes that cause human hypertension, a condition brought about by a collision of Paleolithic genotypes with modern environments.\(^6\)

Models are useful only so far as what is being modeled is known: they are "a simplified or idealized description or conception of a particular system, situation, or process."\(^6\) This is the type of model Guyton and colleagues constructed and his successors elaborated, a mathematical representation of circulatory physiology. By this definition, inbred animal strains are not models of hypertension: at best they are mimics. What they mimic is blood pressure, and it is not to be expected that they are accurate replicas of either human genetics or physiology. In the case of nondipping and circadian sodium excretion, for example, rats are particularly poor model organisms, as their sleep cycle is reversed compared with that of humans. We are now capable of investigating the human genome directly and thoroughly, and the time is right to return hypertension gene discovery to studies of humans.

**Perspectives**

Sodium and water homeostasis has been a physiological priority, because our predecessors exited the marine environment, and structures, functions, and behaviors that contributed to reproductive success by maintaining sodium balance were subject to positive natural selection during evolution. Although sodium deficiency was the primary challenge of terrestrial organisms during evolutionary time, modern humans now contend with chronic sodium excess, and systems originally preserved for sodium retention must now defend against sodium overload. We suggest that nondipping of blood pressure, enhanced nocturnal sodium excretion, and sodium sensitivity of blood pressure are manifestations of an intermediate stage in the evolution of hypertension during aging.

When young normotensive subjects with normal renal function are challenged with a sodium load, sodium balance is usually quickly restored by suppression of renal tubular reabsorption by humoral and paracrine mechanisms without any need to raise blood pressure; such responses are essentially the mirror image of those evolutionarily preserved responses adapted for sodium conservation. Because the range of most individual's sodium excretory capacity is great,\(^6\) the bulk of any dietary sodium ingested is excreted during the day, and a normal diurnal rhythm of sodium excretion is maintained. With aging or renal damage or because of interindividual genetic or developmental differences in renal sodium excretory capacity, the plasticity of renal responses declines, but sodium balance can be efficiently maintained by raising blood pressure. Blood pressure–dependent natriuresis is initially limited to nighttime and manifests as nondipping of blood pressure, an increased rate of nocturnal sodium excretion, and a reversal in the diurnal rhythm of sodium output. When humoral and transient nocturnal pressor mechanisms can no longer maintain sodium balance, the operating set point of pressure natriuresis shifts to a higher range throughout the day and night, and sustained hypertension results.

Because this sequence of adjustments progresses throughout life, we believe that the character of the initiating events may be obscured. We, therefore, propose that more attention should be paid to the nexus of nocturnal sodium excretion, nondipping, and sodium sensitivity in studies of how genetic and environmental determinants initiate the development of hypertension.
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None.

References


