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REVIEW SERIES

Salt sensitivity and circadian rhythm of blood pressure: the keys to connect CKD with cardiovasucular events

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In healthy subjects, blood pressure (BP) drops by 10–20% during the night. Conversely, in patients with the salt-sensitive type of hypertension or chronic kidney disease, nighttime BP does not fall, resulting in an atypical pattern of circadian BP rhythm that does not dip. This pattern is referred to as the 'non-dipper' pattern. Loss of renal functional reserve, due to either reduced ultrafiltration capacity or enhanced tubular sodium reabsorption, induces the salt-sensitive type of hypertension. When salt intake is excessive in patients with salt-sensitive hypertension, the defect in sodium excretory capability becomes evident, resulting in elevated BP during the night. This nocturnal hypertension compensates for diminished natriuresis during the daytime and enhances pressure natriuresis during the night. Nocturnal hypertension and the non-dipper pattern of circadian BP rhythm cause cardiovascular events. When excess salt intake is loaded in patients who are in a salt-sensitive state, glomerular capillary pressure is also elevated, resulting in glomerular sclerosis and eventual renal failure. In this way, salt sensitivity and excess salt intake contribute to both cardiovascular and renal damage at the same time. We propose that salt sensitivity of BP and excess salt intake have important roles in the genesis of the cardiorenal connection. Salt sensitivity and circadian rhythm of BP are the keys to understanding the connections between cardiovascular and renal complications.
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Keywords: circadian rhythm; kidney; natriuresis; non-dipper; salt

INTRODUCTION

High blood pressure (BP) is one of the strongest risk factors for cardiovascular disease.[1] Kidneys are considered the essential organ to control BP, and it seems impossible to cause hypertension without a disturbance in renal function.[2–9] Therefore, we may conclude that most cardiovascular diseases originate from renal dysfunction. Microalbuminuria involves the excretion of a small quantity of albumin into the urine. The condition has attracted attention as a predictor of future nephropathy in diabetes mellitus and is now widely accepted as a risk predictor for cardiovascular events in hypertension and among the general population.[10–14] Albuminuria is considered as a risk predictor rather than a risk factor because the precise mechanisms by which albuminuria causes cardiovascular events remain unknown. Conversely, in patients with renal dysfunction, even mild cases, cardiovascular events occur as frequently as in patients with previous myocardial infarction and diabetes mellitus.[15–18] These findings lead us to assume that chronic kidney disease (CKD), defined as the presence of proteinuria or renal dysfunction for more than 3 months,[19] seems to be a strong risk factor or predictor of cardiovascular events.

In this review, we discuss the mechanisms underlying connections between the cardiovascular and renal systems, with regard to the salt sensitivity and circadian rhythm of BP.

SALT SENSITIVITY AND CARDIOVASCULAR EVENTS

We have shown that salt sensitivity of BP is an independent prognostic factor in essential hypertension.[20,21] A total of 156 patients with essential hypertension were placed on a high-salt (12–15 g NaCl per day) diet and on a low-salt (1–3 g per day) diet for 1 week each in randomized order to determine salt sensitivity.[20,22–25] Patients were then followed up for 7.3 ± 4.3 years until the occurrence of end points such as ischemic heart disease or stroke. Patients whose BP was lowered more than 10% by salt intake restriction were considered to be salt sensitive (n=62); the other patient population was considered non-salt sensitive (n=94). During the follow-up period, cardiovascular events occurred in 14 cases (including 3 fatal events) in the non-salt-sensitive group; cardiovascular events occurred in 17 cases (5 fatal) in the salt-sensitive group. There were two cardiovascular morbid events per 100 patient-years in the non-salt-sensitive group and 4.3 in the salt-sensitive group. The cardiovascular morbid event-free survival curve was significantly worse in the salt-sensitive group. Cox's proportional hazards model identified salt sensitivity as an additional risk independent of BP level, smoking and hypercholesterolemia. These results show that cardiovascular morbidity was higher in the salt-sensitive type of essential hypertension than in the non-salt-sensitive type. This finding has been confirmed by Weinberger *et al.*,[26]

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who showed that even in normotensive subjects salt sensitivity is an independent risk factor for cardiovascular events.

Salt sensitivity is controlled by the kidneys,[7,24,27] and BP characterized by high salt sensitivity indicates a loss of renal functional reserve.[7,28] BP becomes salt sensitive when the ultrafiltration capability of the glomerulus is reduced, as seen in CKD, or when renal tubular reabsorption of sodium is enhanced, as seen in primary aldosteronism, diabetes mellitus and metabolic syndrome.[7,29] Glomerular filtration rate (GFR) is usually reduced in CKD but enhanced in primary aldosteronism, diabetes mellitus and metabolic syndrome. It should be noted here that salt sensitivity of BP is enhanced even in patients whose GFR is elevated when tubular sodium reabsorption is augmented.

SALT SENSITIVITY AND CIRCADIAN RHYTHM OF BLOOD PRESSURE

There is a close relationship between salt sensitivity of BP and the non-dipper pattern of circadian BP rhythm[29–31] (Figure 1). In patients with high salt sensitivity, the nocturnal dip in BP is diminished irrespective of the mechanisms causing salt sensitivity. For example, in both the salt-sensitive type of essential hypertension[32,33] and primary aldosteronism,[34] in which reduced ultrafiltration capability and enhanced tubular sodium reabsorption, respectively, cause salt sensitivity,[7,24,27,35,36] non-dipper patterns of circadian BP rhythm are observed.[29,30]

The circadian rhythm of urinary sodium excretion rate was compared between two groups with different circadian BP rhythms.[37] In dippers, the night/day ratios of both BP and sodium excretion were less than 0.9, even when patients were on a high-salt diet, exhibiting normal circadian rhythms with nocturnal dips. In non-dippers, however, these ratios were significantly higher than in dippers. In particular, the night/day ratio of sodium excretion was greater than 1 in non-dippers, indicating that urinary sodium excretion was enhanced during the night. Salt restriction significantly lowered the night/day ratios of both BP and sodium excretion in non-dippers, whereas these ratios remained unchanged and below 1 in dippers, independent of the amount of salt intake.[37]

There was a strong positive relationship between night/day ratios of BP and sodium excretion observed in patients on a high-salt diet[37,38] but not in patients on a low-salt diet,[37] suggesting that sodium excretion was dependent on systemic BP in patients with high-salt intake (especially in non-dippers), but not in patients with low-salt intake. It is clear now that in patients with salt-sensitive BP, the circadian rhythms of both BP and urinary sodium excretion were all disturbed.[30,37,38] Salt restriction restored these rhythms from non-dipper to dipper patterns.[30,32–34,37]

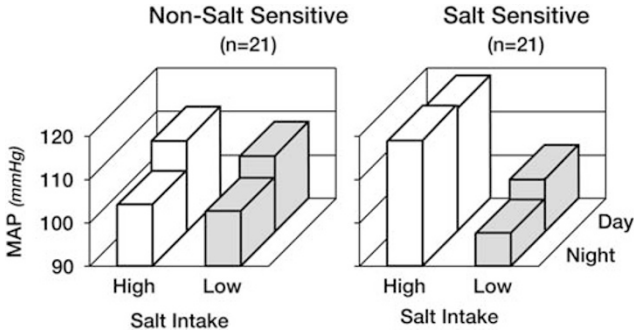

Figure 1 Effects on mean arterial pressure of salt intake restriction and nocturnal drops in non-salt-sensitive (left panel) and salt-sensitive (right panel) types of essential hypertension. Two-way analysis of variance clearly showed that diminished nocturnal BP decline was restored by salt restriction, and the circadian rhythm of BP was shifted from the non-dipper pattern to the dipper pattern in this type of essential hypertension. MAP, mean arterial pressure. Modified from Uzu *et al*.[33]

RENAL DYSFUNCTION AND NON-DIPPER CIRCADIAN RHYTHMS

Because glomerular filtration capability is one of the major factors determining salt sensitivity,[7,24,28,36] the nocturnal dip in BP may be less pronounced as a function of GFR loss. We recently showed this quantitative relationship in CKD[38,39] and healthy donors after nephrectomy,[40] in both of whom there was an inverse relationship between GFR and the night/day ratio of BP. These findings are compatible with high salt sensitivity of BP in glomerulopathy, even when GFR is maintained at a relatively normal level,[41,42] ultimately becoming much higher as renal function deteriorates.[43,44] These findings are also compatible with the proposal that as the number of nephrons is reduced BP becomes more salt sensitive.[7,35,45,46] Alternatively, the non-dipper pattern of circadian BP rhythm is often considered to be a risk factor for the progression of nephropathy.[47–52] Because the degree of non-dipping was closely correlated with the degree of renal function loss, as discussed above,[38,40] however, non-dipping might be consequently correlated with the progression of nephropathy. Our clear results especially obtained after kidney donation[40] that instead it might be a phenotype of renal functional loss, together with well known facts that in patients with renal dysfunction the nocturnal BP dip is lost and circadian rhythms manifest as those of non-dippers,[38,40,47,50,53,54] suggest that the circadian rhythm of BP is determined mostly by the kidneys. The importance of kidneys in the genesis of circadian BP rhythm is consistent with reports that the circadian rhythm of BP is normalized from non-dipper to dipper after kidney transplantation,[55] and also by salt intake restriction and diuretics.[33,34,56–58]

In most non-dippers with essential hypertension, CKD, diabetes mellitus or primary aldosteronism, renal functional reserve is impaired.[28–30] In rare cases, a non-dipper pattern is caused by something other than kidney function (Table 1), such as sleep apnea syndrome, stroke or working a day–night shift, which disturbs sleeping rhythm. Furthermore, disorders such as pheochromocytoma and Cushing syndrome disturb the secretion rhythms of BP-regulating

Table 1 Theoretical classification of disorders causing non-dipper pattern of circadian blood pressure rhythm

Pathophysiology	*Mechanisms*	*Disorders*
Disturbance in sleeping rhythm		Sleep apnea syndrome
		Stroke
		Day–night shift workers
Disturbance in secretion rhythm of vasoactive hormone		Pheochromocytoma
		Cushing syndrome
Impaired renal capacity to excrete sodium (salt-sensitive hypertension)	Reduced ultrafiltration capability	CKD
		Hypertension in black
		Salt-sensitive type of essential hypertension
	Enhanced tubular sodium reabsorption	Primary aldosteronism
		Diabetes mellitus
		Metabolic syndrome

Abbreviation: CKD, chronic kidney disease.
Orthostatic hypotension must be deleted from this list, because BP is totally dependent on the position of the body rather than circadian rhythm of life. Reproduced from Kimura.[29]

hormones, including catecholamine and corticosteroid. Many diseases causing orthostatic hypotension must be excluded from the list of non-dippers because BP is completely dependent on the position of the body but not on circadian rhythm of life.[29]

MECHANISMS UNDERLYING THE NON-DIPPER PATTERN OF CIRCADIAN BP RHYTHM

Our recent studies[29] suggest that diminished renal sodium excretory capability, recognized in the salt-sensitive type of hypertension and CKD, determines the circadian rhythm of BP. When salt intake is high, the defect in sodium excretory capability becomes evident, resulting in elevated nighttime BP. This non-dipper pattern compensates for diminished natriuresis during the daytime and enhances pressure natriuresis during the night. Conversely, when salt intake is low, the defect remains latent, resulting in lowered BP during the night, that is, the dipper profile. If pressure natriuresis during the night compensates for reduced sodium excretion from the kidneys during the daytime, high BP may continue during the night until enough excess sodium is excreted in the urine. Therefore, as renal function deteriorates, more time may be required to excrete sodium by pressure natriuresis during the night before BP begins to dip.[31,59] We examined whether the time period, defined as 'dipping time', until nocturnal mean arterial pressure fell below 90% of the daytime average, became longer as renal function deteriorated. BP profiles during the night were compared among three groups of patients with CKD with different levels of renal function[59] (Figure 2). In the first tertile with relatively normal GFR, BP dropped below 90% of daytime averages soon after the patient fell asleep. In the third tertile with advanced renal dysfunction, on the other hand, BP remained elevated above daytime averages throughout the night. BP in the second tertile was intermediate to that observed in the first and third tertiles. The duration until nocturnal BP fell was inversely correlated with GFR and positively correlated with night/day ratios of mean arterial pressure and natriuresis.

These findings show that BP takes longer to drop during the night among patients with renal dysfunction. This is an essential component of the non-dipper pattern of the circadian BP rhythm. Dipping time may represent a novel index with which to quantify the circadian BP rhythm.

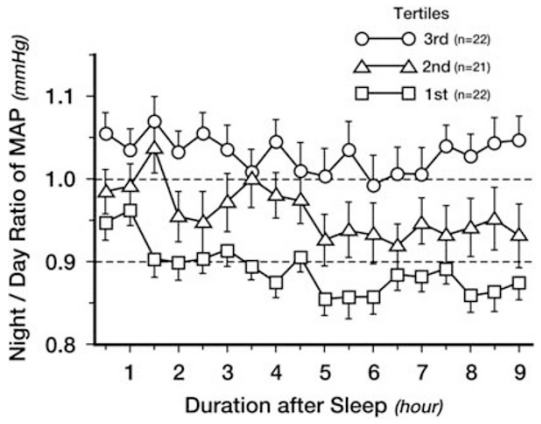

Figure 2 Blood pressure profiles during the night. Ordinate indicates the nocturnal mean arterial pressure (MAP) as the ratio of daytime averages. Subjects were divided into three groups with different levels of renal function based on creatinine clearance (Ccr ml min^{-1}): first tertile (Ccr, 91–164; n=22), second tertile (Ccr, 50–90; n=21) and third tertile (Ccr, 5–41; n=22). As renal function deteriorated from the first tertile to the third tertile, nighttime blood pressure exceeded daytime averages and rarely fell below 90% of the daytime averages during sleep. Error bars indicate the upper and/or lower half of standard error. Modified from Fukuda *et al*.[59]

SALT SENSITIVITY AND STROKE

In addition to the non-dipper pattern, the salt sensitivity of BP is closely linked to glomerular capillary hypertension[28,46,60] and insulin resistance.[61–66] The non-dipper pattern,[67–73] microalbuminuria[74,75] (a marker for glomerular capillary hypertension),[76,77] insulin resistance and metabolic syndrome[78–81] are all known to be strong risk factors for cardiovascular events. Therefore, in the salt-sensitive state, several risk factors are clustered together, leading to future cardiovascular events and renal failure.[20,21,26,82–86]

In our follow-up study[20] of essential hypertensive patients with known salt sensitivity, 31 cardiovascular events were documented during the follow-up period. Of these, 21 were stroke.[20] Conversely, it has been reported that hypertensive subjects with high plasma renin activity, especially white men, are more likely to have subsequent myocardial infarction.[87,88] Because, in general, high plasma renin is associated with low salt sensitivity (non-salt sensitivity) and low renin is associated with high salt sensitivity, the reports cited above seem to contradict our hypothesis. However, the authors[87,88] stated clearly that stroke was not associated with high plasma renin and speculated that there were differences in the etiology of coronary heart disease and stroke, or, alternatively, different relationships between the renin–angiotensin system and the coronary and cerebral vasculatures, respectively. Therefore, the discrepancy between previous reports[87,88] and our hypothesis may be ascribed to the difference in cardiovascular events (for example, coronary heart disease or stroke) or in race (white or Japanese). It is also interesting that high salt sensitivity is more common in people of Japanese origin, and strokes are seen more frequently than ischemic heart disease. Similarly, people of African origin are more salt sensitive than Caucasians,[89,90] and strokes are known to be more common in the former group.[91,92] Thus, there may be a link between salt sensitivity and stroke among Japanese and African Americans.

Primary aldosteronism is one of the most typical forms of salt-sensitive hypertension.[3,34,93] We found 9 cases (15.5%) of stroke in 58 patients with primary aldosteronism,[94] which is consistent with other reports.[95] These findings support our proposal for an association between the salt-sensitive type of hypertension and stroke. It should be noted that the incidence of stroke in patients with primary aldosteronism was approximately twice if proteinuria was present.[94]

CKD AND STROKE

In CKD (one of the major forms of salt-sensitive hypertension) with estimated GFR less than 60 ml min^{-1} per 1.73 m^2, stroke incidence was reported to be increased in the Tsukuba study.[96] It should be emphasized, on the other hand, that the incidence of coronary heart disease did not increase.[96] On the contrary, the Hisayama study[97] showed the different findings because in men the incidence of stroke was not increased, whereas the incidence of coronary heart disease was increased in CKD. In women, on the other hand, the incidence of stroke due to cerebral infarction was significantly increased, but the incidence of coronary heart disease was not increased, which is consistent with the findings by the Tsukuba study. In the Hisayama study, the reason creating such gender difference was not discussed, and the total number of cardiovascular events was increased in CKD only in women. Therefore, these findings obtained in both Tsukuba and Hisayama studies may consistently suggest that that the frequency of stroke is increased in CKD. Whether the incidence of coronary

heart disease is also increased in CKD among Japanese must be studied further.

PATHOPHYSIOLOGY OF THE CARDIORENAL CONNECTION

The remarkable increases in cardiovascular events among hemodialysis patients are widely recognized.[98–101] It is important to understand the precise mechanisms underlying the increase in cardiovascular events as renal function deteriorates and the capacity to excrete sodium into the urine is impaired, even in mild degree.[13,17,102]

As discussed above, the incidence of stroke is increased in both salt-sensitive hypertension and CKD. Bongartz *et al.*[103,104] have proposed that cardiovascular overload due to renal dysfunction and heart failure induces an imbalance between nitric oxide and oxidative stress as well as mild inflammation and activates the sympathetic nervous as well as tissue renin–angiotensin[105] systems, eventually resulting in cardiovascular events. Because pressure overload in the systemic circulation is the first trigger according to the accepted hypothesis, it is easy to understand that stroke and heart failure are frequently associated in patients with salt-sensitive type of hypertension and non-dipper pattern of circadian BP rhythm. In fact, the cumulative incident rate of heart failure was significantly higher in non-dipper than in dippers,[106] which is consistent with the hypothesis. This hypothesis may also explain why inhibitors of the renin–angiotensin system efficiently prevent cardiovascular events, especially in patients with CKD[15,107] and high salt sensitivity.

We propose that salt sensitivity of BP and excess salt intake have an important role in the genesis of cardiorenal connections (Figure 3). When either glomerular ultrafiltration capabilities are reduced or tubular sodium reabsorption is enhanced, BP becomes salt sensitive and glomerular capillary pressure is elevated. Therefore, load to the glomerulus is increased, resulting in glomerular sclerosis and eventual renal failure. In addition, the circadian BP rhythm becomes the non-dipper pattern to enhance pressure natriuresis during the night, whereas nocturnal hypertension causes cardiovascular events. In this way, salt sensitivity and excess salt intake contribute to the cardiorenal connection. Because pressure overload is increased in salt-sensitive hypertension, it is easy to understand why stroke, heart failure and renal failure are frequently associated with renal dysfunction. However, it is difficult to understand why coronary heart disease is also frequently associated with renal dysfunction. The mechanisms explaining how cardiovascular events are increased as renal function deteriorates may differ in stroke and coronary heart disease. The renin–angiotensin system and atherosclerosis may have major roles in coronary heart disease.

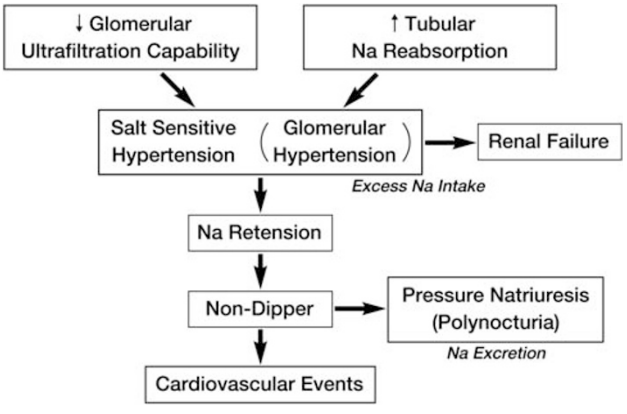

Figure 3 Cardiorenal connection and salt sensitivity of blood pressure. We propose that blood pressure (BP) salt sensitivity and excess salt intake have an important role in the genesis of a cardiorenal connection. When glomerular ultrafiltration capabilities are reduced or tubular sodium reabsorption is enhanced, BP becomes salt sensitive and glomerular capillary pressure is elevated. Therefore, the glomerular load is increased, resulting in glomerular sclerosis and eventual renal failure. In addition, circadian BP rhythm becomes non-dipper to enhance pressure natriuresis during the night, whereas nocturnal hypertension causes cardiovascular events. In this way, salt sensitivity and excess salt intake contribute greatly to the cardiorenal connection.

CONCLUSION

Salt intake restriction has been considered one of the most important lifestyle modifications in the field of hypertension and renal diseases.[108] Nevertheless, there is no consensus on its importance in arresting cardiorenal complications. As discussed above, salt restriction in patients with high salt sensitivity may lower systemic and glomerular capillary pressure, reduce proteinuria and normalize circadian BP rhythm from a non-dipper pattern to a dipper one. Therefore, salt restriction may relieve these risks and prevent cardiovascular and renal diseases. We believe that both salt sensitivity and a non-dipper pattern of circadian BP rhythm must be recognized as important prognostic predictors for cardiorenal diseases. Salt sensitivity and a non-dipper pattern reflect the loss of renal functional reserve and severity of hypertension that cannot be predicted by classic factors such as BP itself, risk factors and target organ damage.

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