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# The complex relationship between chronic kidney disease and ambulatory blood pressure patterns

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## Abstract

Hypertension and chronic kidney disease (CKD) frequently coexist, and both are risk factors for cardiovascular events and mortality. Among people with hypertension, the loss of the normal fall in nighttime BP, called nondipping, can only be diagnosed by ambulatory BP monitoring (ABPM), and is a risk factor for cardiovascular events. The pathophysiology of nondipping is complex, and CKD is an independent risk factor for non-dipping. In fact, non-dipping can be seen in as many as 80% of people with CKD. However, the evidence for nondipping as an independent risk factor or causal agent for adverse outcomes in CKD remains mixed. ABPM has been shown to be superior to clinic BP measurement for correlating with end organ damage and prognosis in CKD. This review covers the evidence for the use of ABPM in CKD, the evidence linking ABPM patterns to outcome in CKD, and the evidence for treatment of nondipping in CKD.

## INTRODUCTION

Hypertension and chronic kidney disease (CKD) are both common in the general population. Community based surveys in the United States such as the National Health and Nutrition survey (NHANES) indicate the prevalence of hypertension at 30%[1] and CKD at 13%[2] Similarly, both hypertension[3] and CKD[4;5] are major risk factors for cardiovascular disease. What makes hypertension particularly dangerous is that it frequently coexists with CKD; this is because it is both a consequence and a cause of CKD. A recent cohort study reported 86% of CKD patients had hypertension while 58% of those hypertensives were treated with 3 or more medications.[6] Furthermore, among >330,000 men screened for the Multiple Risk Factor Intervention Trial (MR FIT) increasing BP showed a graded increase in the risk of end stage kidney disease (ESKD) with an over 20 fold increase in risk of ESKD for those patients with the highest BP as compared to those with normal BP despite adjustment for baseline kidney function.[7]

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Ambulatory BP monitoring (ABPM) is the recognized gold standard for the assessment of hypertension,[8] and ABPM patterns have been established as having prognostic importance in the general hypertensive population with a particular interest on nighttime blood pressure. Isolated nocturnal hypertension, defined as nighttime BP ≥ 120/70 mmHg despite normal daytime BP has been associated with both cardiovascular events and mortality.[9] Normally nighttime BP falls roughly 15% in both normotensive and hypertensive patients, which is termed dipping.[10] The lack of a normal fall in BP is termed nondipping, and is typically defined as an average nighttime BP drop less than 10% from the daytime average. In the hypertensive population nondipping has also been shown to be a risk factor for cardiovascular events.[11;12]

On account of the high prevalence of hypertension and the high cardiovascular morbidity in CKD, the use of ABPM is of particular interest in the CKD population. This review will cover the evidence for the use of ABPM in CKD, with a particular focus on the BP patterns seen on ABPM. We do not discuss ambulatory BP patterns among patients on dialysis or those who have been transplanted.

## UTILITY OF AMBULATORY BLOOD PRESSURE MONITORING IN CKD

Clinic BP measurements frequently both overestimate and underestimate true BP in the general hypertensive population,[13;14] and this discrepancy shared by people with CKD. White coat hypertension is defined as elevated clinic BP but controlled BP out of the office, whereas masked hypertension is defined as controlled BP in the office with elevated BP out of the office. Among 980 people with CKD, a meta-analysis of 6 studies found a prevalence of 28% for white coat hypertension and 8% for masked hypertension.[15] Alarmingly 40% of those subjects deemed to be normotensive or to have controlled hypertension actually had elevated BP out of the office, making them masked uncontrolled hypertensives. Similarly, a high rate of masked hypertension was observed in the follow up cohort study of the African American Study of Kidney Disease (AASK) where 61% of the 617 participants had controlled clinic BP but of those fully 70% had masked hypertension using a definition of hypertension by ABPM that included night time BP.[16]

### End Organ Damage

In cross sectional studies of CKD patients ABPM is superior to clinic BP measurements for correlating with end organ damage. This is true for markers of kidney damage, such as proteinuria, wherein a cross-sectional study of 232 CKD patients found ABPM is more strongly associated with proteinuria than was clinic BP.[17] ABPM is also more strongly associated with echocardiographic left ventricular hypertrophy than is clinic BP, as shown in studies of disparate CKD populations such as (i) a study of 85 CKD patients without diabetes or history of cardiovascular disease,[18] (ii) in a study of 26 normotensive patients with polycystic kidney disease,[19] (iii) and in 599 CKD patients from the AASK cohort study.[20]

### Prognosis

The current evidence supports the superiority of ABPM over clinic BP for predicting prognosis in CKD, including renal endpoints, cardiovascular endpoints, and mortality. In a study of 75 patients with type I diabetes mellitus ABPM was superior to clinic BP in predicting development of microalbuminuria over a mean of more than 5 years of follow up.[21] ABPM also significantly predicted decline of kidney function in small or retrospective studies of IgA glomerulonephritis,[22] diabetic kidney disease,[23] as well as general CKD.[24;25] More recently larger prospective studies have shown ABPM to be superior to clinic BP for predicting outcomes, including in a cohort study of 217 patients with CKD who were followed for a median of 3.5 years and examined for a composite endpoint of death or ESKD.[26] Similarly, a recent cohort study of 436 CKD patients followed for a median of 4.2 years found ABPM to be superior to office BP for predicting cardiovascular events or the composite of death and ESKD.[27] Most recently, an analysis of 617 CKD patients in the AASK cohort study found ABPM to be superior to office BP for predicting both cardiovascular events and a composite of death, ESKD, or doubling of serum creatinine over a median follow up of 5 years.[28]

## NONDIPPING IN CKD

ABPM patterns in CKD can be been described by the dichotomous characterization of either dipper or nondipper status; nondipping is defined as nighttime systolic BP average <10% lower than the daytime BP average. Although the preponderance of investigation has focused on the dichotomous dipper categorization, a more complicated continuous model has been proposed that fits a sinusoidal curve to describe the diurnal BP pattern. Using this model three types of BP patterns can be described: 1) in phase with BP falling during sleep; 2) out of phase with BP rising during sleep; or 3) phase-less with only a small amplitude of BP variation without a clear rise or fall in BP.[29]

The prevalence of nondipper status has previously been noted to be inversely related to kidney function, exemplified in a retrospective study of 380 patients where 82% of those patients with ESKD on dialysis were nondippers.[30] In the 617 patients of the AASK cohort study 80% were nondippers.[16] More recently a large cross sectional study reported on the prevalence of nondipping in hypertensive CKD.[31] This study included 10,271 patients referred for ABPM in northwest Spain who were enrolled in the Hygia Project, a study of ABPM and BP treatment to reduce cardiovascular events. All patients were hypertensive by 48 hour ABPM criteria, and 3,227 patients had CKD defined as estimated glomerular filtration rate (GFR) < 60 mL/min/1.73m$^2$ or microalbuminuria on 2 occasions at least 3 months apart. The authors report a nondipper prevalence of 61% in those hypertensive patients with CKD versus 43% in those hypertensive patients without CKD. Additionally they reported a significant increase in the proportion with nondipper status with each increasing stage of worsening CKD.

Although, progressive fall in GFR is associated with greater prevalence of non-dipping, in cross-sectional surveys, it is evident that even minimal degrees of proteinuria are associated with profound perturbations in circadian rhythms. In fact, at any given stage of CKD, those

with greater proteinuria have less dipping. Once proteinuria is accounted for, the association of CKD with non-dipping is significantly weakened.

## Physiology of Dipping

The normal circadian variation in BP was accurately described over 30 years ago using 48 hour continuous ambulatory intra-arterial BP monitoring, which identified the normal BP peak in the mid-morning, the nighttime dip in BP, and the morning surge in BP prior to awakening.[32] Three primary factors mediate dipping: autonomic nervous system function, sleep-activity cycle, and sodium sensitivity.

**Autonomic Function—**Regulation of the body's normal circadian rhythm starts in the brain's suprachiasmatic nucleus and includes the pineal gland, the hypothalamus, and the pituitary gland as well.[33] However, the final common pathway in the circadian rhythm of BP appears to be the symphathetic nervous system. Multiple investigations have shown the importance of the sympathetic nervous system including alpha-adrenergic regulation for the circadian change of vascular tone[34], circadian variation in levels of both norepinephrine and epinephrine mirroring the change in BP,[35] and muscle sympathetic nerve activity correlating with nocturnal dipping of BP.[36] Perhaps most compelling are observations that circadian variation in BP is lost in patients with quadriplegia from cervical spinal cord injuries, whereas it is preserved in paraplegic patients with thoracic cord injuries,[37;38] thus suggesting that central sympathetic control is necessary for normal circadian change in BP. Provoked by sympathetic activation, the reninangiotensive-aldosterone system is an important regulator of normal BP pattern, and renin, aldosterone, and angiotensin II have all been shown to exhibit a circadian pattern similar to that of BP.[39;40]

**Sleep-Activity Cycle—**As would be expected intuitively, behavior also significantly impact the normal circadian change in BP with physical activity explaining a large proportion of the circadian variation of BP.[41] Similarly, wakefulness and sleep impact BP pattern, as sleep deprivation is associated with increased sympathetic activity[42;43] and nondipping has been positively correlated to the apnea-hypopnea index used to grade sleep disordered breathing.[44]

**Sodium Sensitivity—**Nondipping has been associated with sodium sensitivity in hypertensive patients,[45] and both sodium restriction[45;46] and thiazide diuretics[47] have been shown to restore dipping in these salt sensitive patients. Potential mechanistic links between salt sensitivity and nondipping include impaired baroreflex function leading to sympathetic activation[48] and impaired endothelial function, which is both common in nondippers[49] and which has been shown to be associated with salt sensitivity in an animal model.[50]

With the above in mind the high prevalence of nondipping in CKD should come as no surprise, in particular because CKD is well known to be associated with increased sympathetic activation.[51] Additionally, obstructive sleep apnea,[52] sedentary lifestyle,[53] and poor sleep quality[53] are all common in CKD, with the latter possibly driven by nocturia that is itself associated with nondipping in CKD[54]. However, an interesting of study of 14 highly selected hemodialysis patients and 14 matched controls suggests that comorbidities

contribute significantly to the prevalence of nondipping in CKD.[55] Patients were meticulously selected to exclude putative causes of nondipping including diabetes, hypertension, heart failure, inability to walk, psychiatric disease, irregular sleep schedule, and even the use of erythropoietin. On investigation these hemodialysis patients all had normal circadian BP variation, which was identical to the matched controls.

## Dipping and Outcomes

While nondipping is considered a marker of increased cardiovascular risk in the general hypertensive population, the evidence for nondipping as an independent risk factor for adverse outcomes in CKD is less certain. Nondipping has been recognized as a risk factor for progression of CKD,[22;23;25] however none of these studies controlled for the presence of albuminuria or proteinuria, which is both associated with nondipping and is a well-established risk factor for worsening of CKD.[17] Therefore it is possible that nondipping in itself is not a cause of accelerated progression of CKD, but rather that nondipping is a marker of a more proximal pathologic process that also accelerates the progression of CKD. Similarly, when nondipping has been investigated as a risk factor for the hard endpoints death, ESKD, or cardiovascular events it loses its significance when daytime BP or 24 hour BP is considered, or when other known cardiovascular risk factors are considered.[26;28;56;57] One notable exception is the recent cohort study of 436 CKD patients where nondipping was shown to be a significant risk factor for both ESKD and cardiovascular events, despite adjustment for 24 hour BP, proteinuria, cardiovascular history, and other risk factors.[27]

It is not clear why the association between nondipping and cardiovascular events in CKD seems weaker than in the general hypertensive population, but one explanation may be the limited reproducibility of the dipping phenomenon. In one study of paired 24 hour ABPM examinations 4 weeks apart in 65 CKD patients, 23% changed dipping status between studies and the κ statistic of reproducibility was only 0.415.[54] Similarly, when 24 hour ABPM was performed serially in 4 month intervals in 34 CKD patients the dipping status changed in 38% of paired examinations.[58] This may be on account of a combination of the poor sleep experienced by CKD patients[53] coupled with the ABPM procedure itself as it is associated with reduced daytime activity and poorer sleep,[59] both of which would be expected to reduce dipping. To improve reproducibility, routine 48 hour ABPM has been suggested as an alternative to 24 hour ABPM, and while 48 hour ABPM has been shown to reduce variability, it has not yet been shown to improve reproducibility.[60]

## Interventions for Nondipping

If nondipping BP pattern is a cause of adverse outcomes in CKD, then treatment of nondipping may improve outcomes. The first question is whether dipping can be restored in nondippers with CKD. A recent cross sectional study of 48 hour ABPM in 2,659 patients with CKD from the Hygia Project cohort looked at this question and found that the 1,213 patients taking at least one BP medication at bedtime had a significantly lower prevalence of nondipping at 54% versus the 68% prevalence in the 1,446 patients who took all their antihypertensive medications in the morning.[61]

While cross sectional and prospective observational studies may suggest associations, a causal link can only be established by interventional randomized controlled trials. The earliest uncontrolled trial of changing dose schedule to treat nondipping examined 32 nondipper subjects with CKD.[62] Average estimated GFR was 46 mL/min/1.73m$^2$ and subjects were hypertensive nondippers despite taking an average of 2.4 antihypertensive medications. During the trial one non diuretic antihypertensive medication was changed to be taken at bedtime and 24 hour ABPM was repeated at 8 weeks, and all but 4 of the 32 subjects became dippers. More recently, a randomized controlled open label crossover trial was performed in 147 former subjects from the AASK study with average estimated GFR 45 mL/min/1.73m$^2$ and taking an average of 4.1 antihypertensive medications.[63] Notably, not all subjects were nondippers on 24 hour ABPM; 24% were dippers at baseline. These participants were randomly assigned to one of 3 different antihypertensive regimens: 1) take all once daily antihypertensive drugs in the morning, 2) take all once daily antihypertensive drugs at bedtime, or 3) take all once daily antihypertensive drugs in the morning plus one of diltiazem, hydralazine, or ramipril taken at bedtime. These treatments were continued for 6 weeks and 24 hour ABPM was repeated before changing to the next regimen. The primary endpoint was nocturnal BP and there was no difference between the 3 treatment regimens, furthermore there was no significant interaction effect for dipper status on outcome.

The only randomized trial in CKD patients that has examined change in medication dosing schedule to impact outcomes is the Ambulatory Blood Pressure Monitoring and Cardiovascular Events study (known at MAPEC for the Spanish name Monitorización Ambulatoria de la Presión Arterial y Eventos Cardiovasculares).[64] This Spanish trial enrolled 661 subjects with CKD defined as estimated GFR < 60 mL/min/1.73m$^2$ or microalbuminuria who were also hypertensive by 48 hour ABPM criteria. At baseline subjects had an average estimated GFR of 66 mL/min/1.73m$^2$, average 48 hour BP of 135/78 mmHg, and 66% were nondippers. No data are available for baseline number of antihypertensive medications but at the final visit subjects were on 2.2 medications on average. During the trial subjects were randomized to the open label intervention of taking at least one antihypertensive medication at bedtime versus the control of taking all medications in the morning. Subsequently 48 hour ABPM was performed at least yearly, and after a median follow up of 5.4 years the intervention group had a significant improvement in nighttime BP and 48 hour ambulatory BP control, as well as a significantly lower proportion of nondipping at 41% versus 71% nondipping in the control group. Most notably, the composite endpoint of death or cardiovascular events had a highly significant hazard ratio of only 0.31 in the intervention group with a relative risk reduction of 65%.

The strongly positive outcomes of the MAPEC study are encouraging, but caution must be exercised before a routine recommendation for bedtime dosing of antihypertensive medications in CKD can be made. Most notably, the treatment was open label and while the outcome assessors were blinded to the treatment assignment, the treating practitioners were not and furthermore they were aware of ABPM results. Secondly, it is unclear what algorithm the treating practitioners used to manage BP during the follow up period. Therefore it is possible that the positive outcomes associated with the intervention were not due to the intervention itself, but due to a bias in treatment. Additionally, the results of the MAPEC study are divergent from the randomized controlled crossover trial in the AASK

cohort noted above,[63] as well as divergent from the results of the Heart Outcomes Prevention Evaluation (HOPE) trial in subjects with high cardiovascular risk but without overt nephropathy.[65] In the HOPE trial 9,297 subjects were randomized to ramipril at bedtime versus placebo and followed for 5 years for major cardiovascular events including cardiovascular death. A small subset of 38 HOPE subjects were studied with 24 hour ABPM at baseline and at 1 year of participation and those on ramipril had a significant reduction in nighttime BP versus placebo.[66] Ultimately the HOPE trial showed a significant 22% relative risk reduction for major cardiovascular events, which is a far smaller effect than was seen in the MAPEC study.

While we do often dose antihypertensive medications at the bedtime for our CKD patients on account of convenience and patient preference, based on the mixed evidence from randomized trials a recommendation to routinely dose medications at bedtime is difficult until further studies are done in this population. Dosing drugs such as diuretics at bedtime may especially be problematic.

## RECOMMENDATIONS

The gold standard for BP assessment in CKD remains ABPM,[8] which is the only method available to examine circadian change in BP. However, in our research and clinical experience the discomfort of the ABPM procedure and the extra visit to the clinic that is required for analysis limits its applicability in our routine clinical population. While an abnormal circadian BP pattern is very common in the CKD population, which is plausibly linked to the CKD itself or to common comorbidities in this population, it remains to be proven that the loss of normal circadian BP pattern is a treatable cause of the increased cardiovascular risk observed in CKD. It is for these reasons that in our day-to-day management of hypertension in the setting of CKD we predominantly employ home BP monitoring. This method does not elucidate circadian BP pattern, but still it can indicate the presence of white coat hypertension and masked hypertension.[15] Compared to ambulatory BP monitoring, it is simpler and easier for patients to adopt. Importantly, home BP monitoring retains the salutary characteristics of ABPM as compared to clinic BP measurements in CKD including superior prediction of progression of CKD[67;68] and death or cardiovascular events.[26;56] Additionally, recognizing that therapeutic inertia is an established obstacle to adequate management of hypertension,[69-71] home BP monitoring appears useful for overcoming that inertia precluding BP interventions, thereby possibly improving control of hypertension.[72] Accordingly, we endorse the American Heart Association recommendation [73]for the use of home BP monitoring among all people with hypertension and ambulatory BP monitoring for the select few where home BP monitoring is not informative or not feasible.

## CONCLUSION

ABPM is the gold standard for BP assessment and in the CKD population it has been shown to be superior to clinic BP measurement for correlating with end organ damage and prognosis. ABPM is the only method to monitor nocturnal BP and to detect nondipping,

however further randomized trials are needed to establish whether routine use of ABPM will improve hard outcomes in this population.

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