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Ambulatory Blood Pressure in Chronic Kidney Disease

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Abstract Chronic kidney disease (CKD) affects approximately 20 million adults in the United States. Patients with CKD have an increased risk of cardiovascular (CV) disease. Ambulatory blood pressure monitoring (ABPM) provides superior BP measurements when compared to office BP measurements in normotensive, hypertensive and CKD patients. ABPM measurements are often abnormal in CKD, with CKD patients frequently showing an altered circadian rhythm with an increased rate of non-dipping and reverse dipping. The prevalence of non-dippers and reverse-dippers increases progressively as stage of CKD progresses. ABPM has been shown to be a better tool for predicting CV risk, CKD progression, end stage renal disease (ESRD) or death than office-based pressures. ABPM is also additive and adds prognostic value for predicting CKD and CV outcomes when added to estimated glomerular filtration rate (eGFR). Although ABPM is time consuming, it is worth considering, as the data demonstrates that information from ABPM can potentially impact future CV and renal outcomes in patients with CKD.

Keywords Chronic kidney disease · CKD · Ambulatory blood pressure monitoring · ABPM · Hypertension · Cardiovascular risk · Dipping · Reverse dipping

Introduction

Chronic kidney disease (CKD) affects approximately 20 million adults in the United States and the prevalence of CKD continues to increase. Patients with CKD have an increased risk of cardiovascular disease (CVD), and many CKD patients die before reaching the need for dialysis often from CVD [1]. There is constant debate about the optimal blood pressure (BP) goals for the non-dialysis CKD population, with ongoing studies in this area (Systolic Blood Pressure Intervention Trial [SPRINT]) [2]. It is well documented that ambulatory blood pressure monitoring (ABPM) provides superior BP measurements when compared to clinic or office BP measurements in the general population. However, most studies have assessed office BP measurements when evaluating progression of CKD and current BP guidelines for non-dialysis CKD are based on office BP measurements. Abnormal ABPM measurements are commonplace in CKD, and the prognostic value of ABPM for renal and cardiovascular (CV) outcomes are now becoming clearer. This review will focus on the circadian pattern of ABPM in normal, hypertensive and CKD patients, and the role of ABPM in determining CKD progression and CVD risk in the CKD population.

The Circadian Pattern of ABPM: Normal Versus Hypertension Versus CKD

ABPM is undertaken by wearing a device that takes BP measurements over a 24 to 48 hour period, usually every 15 to 20 minutes during the daytime and every 30 to 60 minutes during sleep [3••]. BP follows a similar circadian variation in both normotensive and hypertensive patients with a lowering of BP during sleep, with the lowest BP at 3 am followed by a more abrupt rise during the early hours of the morning before arousal, and the highest BP at mid-morning followed by a progressive fall throughout the day [4]. This has been confirmed in various normotensive and hypertensive populations. Pickering et al. [5] used ABPM in a cohort of 25 normotensive, 25 borderline hypertensive and

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25 established hypertensive subjects who were untreated or off treatments, and confirmed a similar circadian pattern of BP among all three groups, with the highest BP during the day and the lowest BP readings recorded during sleep.

O'brien et al. [6] found that 83 % of a cohort of 123 consecutive hypertensive patients undergoing 24-hour (24-h) ABPM had a difference of 10/5 mmHg or greater between the mean daytime and nighttime BP, and classified them as "dippers". The remaining 17 % of the cohort had a more blunted circadian variation of BP and were classified as "non-dippers". Compared to the dippers, non-dippers had a significantly higher rate of stroke (23.8 % vs 2.9 %), despite having no significant difference in age, sex, weight, daytime systolic and diastolic BP and medications. Data from larger population studies have also demonstrated that nighttime BP drops about 15 mmHg or 10–20 % compared to daytime BP in healthy individuals [7, 8]. Ohkubo et al. [9] obtained 24-h ABPM from 1,542 residents of Ohasama, Japan, who were representative of the Japanese general population and followed their survival for a mean of 9.2 years. They found a linear relationship between the nocturnal fall of BP and CV mortality, independent of the overall 24-h ABPM. On average, a 5 % decrease in the nocturnal fall of BP was associated with an approximately 20 % increase in the risk of CV mortality, even when the 24-h ABPM were in the normotensive range (< 135/80 mmHg). It is worth noting that 22 % of the cohort were hypertensive and 36 % were non-dippers (defined as less than 10 % nocturnal decline in systolic or diastolic BP). Compared to the normotensive group, the hypertensive group had a higher percentage of non-dippers (44 % vs 33 %).

Hypertension is common among patients with CKD and the prevalence of hypertension increases as overall kidney function deteriorates, ranging from 60–100 %, depending on the population studied [10]. In a large cohort of 1795 subjects with varying degrees of impaired renal function, the Modification of Diet in Renal Disease (MDRD) Study showed an 83 % prevalence of hypertension in CKD [11]. The prevalence of hypertension increased from 65 % in patients with normal or near-normal kidney function (with glomerular filtration rate [GFR] around 83 ml/min/1.73 m^2) to over 95 % when GFR was about 12 ml/min/1.73 m^2 [11].

CKD is known to be associated with altered circadian BP rhythm: blunted amplitude of circadian variation as well as increased rates of non-dippers and even reverse-dippers. Portaluppi et al. obtained non-invasive ABPM every 15 minutes for 48 consecutive hours from a group of 30 subjects with hypertension and non-hemodialysis CKD and a matched group of 30 subjects with essential hypertension [12, 13]. While the group with essential hypertension had a peak BP in the early afternoon and a mean nocturnal BP fall of 13 mmHg, the group with CKD had peak BP close to midnight and a mean nocturnal BP increase of 3 mmHg.

In a retrospective study using ABPM in 380 patients with essential hypertension, hypertension with CKD; or end stage renal disease (ESRD) on renal replacement therapy, Farmer et al. [14] found that the non-dipper was significantly more prevalent in patients with CKD (53 %) compared to patients with essential hypertension (30 %). In addition, the prevalence of non-dipper increased progressively as the renal function deteriorated with the prevalence of non-dipper reaching 82 %, 78 %, 75 % and 74 % in patients on hemodialysis, peritoneal dialysis, or with plasma creatinine level above 6.8 mg/dl or a renal transplant, respectively. Another study of 322 elderly veterans with or without CKD [15] showed a similar trend with the CKD group having a significantly higher percentage of non-dippers (75 %) compared to the non-CKD group (56 %).

A recently published large cross-sectional study of 10,271 hypertensive subjects enrolled in the Hygia Project compared the ABPM parameters of hypertensive patients with or without CKD [16•]. Compared to the non-CKD group, the CKD group of 3,227 subjects had significantly higher systolic BP (mainly during the nighttime) and lower diastolic BP (mainly during the daytime), resulting in significantly greater pulse pressure. Consistent with previously published results, the prevalence of non-dippers was significantly higher in the CKD group (60.6 %) compared to the non-CKD group (43.2 %). In addition, the biggest difference between the CKD and non-CKD groups was in the prevalence of reverse-dipper status (i.e. nighttime BP increase rather than decrease) with 17.6 % in the CKD group and 7.1 % in the non-CKD group. The prevalence of reverse-dippers increased progressively from 8.1 % in the stage 1 CKD to 34.9 % in the stage 5 CKD.

In another recent study of 104 CKD patients using ABPM, Mizuno et al. [17•] showed that 51 % of the CKD cohort had morning hypertension (defined as BP exceeded 135/85 mmHg during the first 2 hours after awakening). In addition, the majority of the cohort with morning hypertension had sustained elevation of nighttime BP (defined as no nighttime BP<120/70 mmHg) and high nighttime/daytime BP ratio with only one subject having morning BP surge (defined as BP increase>25 mmHg around the time of awakening or BP increase>55 mmHg from the lowest nighttime BP), suggesting morning hypertension in CKD is the sustained type and not the surge type.

In summary, there are a number of studies using ABPM in the CKD population that demonstrate that CKD patients have an altered circadian BP rhythm when compared to normotensive and hypertensive patients without CKD. In studies specifically using ABPM, there is also an increased rate of both non-dipping and reverse dipping in CKD patients. The characteristics of ambulatory BP findings in subjects with CKD are summarized in Table 1. An example

Table 1 Characteristics of ambulatory blood pressure (BP) in subjects with chronic kidney disease (CKD)

- Altered circadian BP rhythm
- Blunted amplitude of circadian variation
- Increased rate of non-dippers
- Increased rate of reverse-dippers
- Prevalence of non-dipper status increases progressively as stage of CKD worsens
- Prevalence of reverse-dipper status increases progressively as stage of CKD worsens
- Morning hypertension in CKD is sustained, as opposed to surge type of hypertension

of a 24-h ABPM study from a patient with stage 3 CKD is shown in Fig. 1. This figure demonstrates higher mean BP readings at night versus daytime readings and reverse dipping.

The Role of ABPM to CKD Progression

This part of the review will focus on the evidence and studies that have looked specifically at ABPM versus office BP measurements, and how this translates into risk for CKD progression and CV risk. Despite many years of availability of ABPM, there are only a few prospective studies of ABPM in CKD (non-dialysis dependent) specifically investigating the prognostic significance of the 24-h BP profile for renal and CV outcomes. These studies have been performed worldwide in various countries in multiple different population groups.

Minutolo and colleagues evaluated the role of ABPM in patients with non-dialysis CKD stages 2 to 4 at four Italian nephrology units [18••]. This was a prospective cohort study of 436 patients. Patients were followed for a median of 4.2 years after ABPM. The causes of CKD in this population were hypertensive nephropathy (42 %), diabetic nephropathy (20 %) and an amalgam of tubulointerstitial disease and polycystic kidney disease and "other" (20 %). The relatively low percentage of diabetes makes this population a little different from that in the US, for example, where diabetes accounts for about 45 % of the CKD population [19]. All

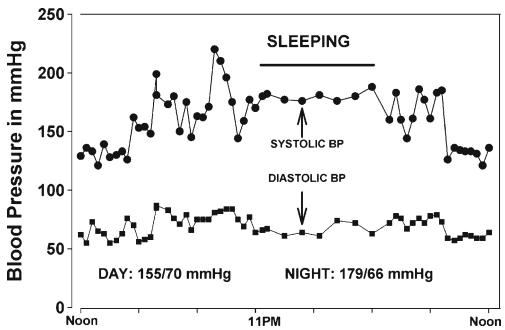

Fig. 1 Example of 24-hour ABPM in a 65-year-old male patient with stage 3 CKD (eGFR of 43 ml/min). Mean daytime BP=155/70 mmHg. Mean nighttime BP=179/66 mmHg. Note: sleep reported from 9.45 pm until 5.30 am. Recording demonstrates higher nighttime BP readings than daytime BP readings with reverse dipping present

patients were repeatedly seen by the same physician, and were followed until they reached a pre-specified renal or CV end point or until September 30, 2010. Primary end points were time to renal death (end-stage renal disease or death) and time to fatal or nonfatal CV events. The mean age ± SD of patients was 65± 13.6 years with a mean glomerular filtration rate of 42.9±19.7 mL/min/1.73 m^2. All the patients were Caucasian and approximately one third had preexisting CV disease. Quintiles of BP were used to classify patients. Mean office BP was 146/82 mmHg, daytime SBP was 131/75 mmHg, and nighttime BP was 122/66 mmHg. A total of 155 patients reached the renal end point and 103 patients reached the CV end point. There are some important findings associated with this study. Office BP values except for the highest quartile were not predictive of either renal or CV end points. Nighttime SBP was a stronger predictor for both end points than daytime SBP readings. There was an increased risk for renal end point with a daytime SBP>135 mmHg and increased CV end point with nighttime SBP>124 mmHg. Nighttime DBP better predicted risk of fatal and nonfatal CV end points. Dipping status was evaluated in all patients and results showed a two-fold increased risk of CV end points in non-dippers and reverse dippers, with risk of renal death increased by 62 % in non-dippers and by 72 % in reverse dippers.

Of note, more than 80 % of these patients had CKD stage 3 or worse. They found that ABPM was a better tool for predicting renal and CV risk than office-based pressures (which had little predictive power unless they were very high). They also noted that the predictive power for ABPM was independent of diabetes, proteinuria, level of hemoglobin and pre-existing CVD. As all of the patients in the study were Caucasian, this may not be generalizable to the US population of CKD patients [20].

Another study by Agarwal confirmed these findings [21]. This study specifically assessed the role of ABPM compared to office BP in predicting ESRD and death in patients with CKD. BP was measured using 24-h ABPM and office BP in a cohort study of 217 US Veterans with CKD. ABPM readings were lower at 134±17/73±11 mmHg compared to office BP readings of 155±26/85±14. The composite renal end point of ESRD or death over a median follow-up of 3.5 years occurred

in 34.5 % of patients (75 patients), death occurred in 24 % (52 patients) and ESRD occurred in 20.2 % (36/178 patients). Thirty-nine patients died before reaching ESRD. Interestingly, one standard deviation (SD) increase in SBP increased the likelihood of the composite outcome to 1.69 (95 % confidence interval (CI) 1.32–2.17) for standard clinic measurement and to 1.88 (95 % CI 1.48–2.39) for ABPM. One SD increase in SBP as measured on ABPM increased the risk of ESRD to 3.04 (95 % CI 2.13–4.35) and to 2.20 (95 % CI 1.43–3.39) when adjusted for standard clinic systolic BP. Non-dipping was also associated with increased risk of total mortality and composite end point. This study reinforces that not only are ABPM measurements better predictors of CKD progression than office BP, they are also stronger predictors of ESRD or death compared to BPs obtained in the office.

A study from Japan examined the CKD risk associated with white coat hypertension and masked hypertension as determined by 24-h ABPM in 1,023 residents in the general Japanese population of Ohasama [22•]. ABPM and office BP readings were recorded and compared. CKD was defined by the amount of positive proteinuria and/or estimated glomerular filtration rate <60 ml/min per 1.73 m^2. Participants were categorized into four groups using daytime ABPM of 140/85 mmHg and office BP of 140/90 mmHg as cutoff points: normal BP – 60.0 %; white coat hypertension – 15.4 %; masked hypertension – 15.0 %; and sustained hypertension – 9.6 %. Odds ratios (ORs) for prevalence of CKD were calculated using a multiple logistic regression model. Compared with normal BP, risk of CKD was significantly higher in sustained hypertension (OR, 2.81; 95 % CI 1.66–4.75; P=0.0001), masked hypertension (OR, 2.29; 95 % CI, 1.45-3.63; P=0.0004) and white coat hypertension (OR, 1.67; 95 % CI, 1.03-2.71; P=0.0368). Masked hypertension and white coat hypertension that could only be identified by performing ABPM were significantly associated with CKD.

Other studies adding more strength to the robustness of ABPM in predicting CKD comes from analysis of data from the (AASK) trial. The primary objective of the AASK study was to identify risk factors for progressive CKD in African Americans with hypertensive CKD [23]. On completion of the AASK Trial, participants who had not yet begun dialysis treatment or undergone kidney transplantation were invited to enroll in a prospective Cohort Study. Between 2002 and 2003, 617 African Americans with hypertensive CKD treated to a clinic BP goal of<130/80 mmHg were enrolled in this prospective, observational cohort study [24].

Analysis was performed of baseline ABPM data from subjects in the AASK Disease Cohort Study in subjects with controlled clinic BP (< 140/90 mmHg) [25]. Masked hypertension was defined by elevated daytime (≥ 135/85 mmHg) or elevated nighttime (≥ 120/70 mmHg) ABPM in those with controlled clinic BP (< 140/90 mmHg). Of the 61 % (377/617) of participants with controlled clinic BP, 70 % had masked hypertension. Compared with those with controlled clinic BP or white coat hypertension, target organ damage assessed cross-sectionally (proteinuria and left ventricular hypertrophy) was more common in those with elevated nighttime BP, masked hypertension, or sustained hypertension. Masked hypertension, particularly nocturnal BP control, may account for the disappointing results from the AASK study where despite excellent in-office BP control there was still progression of CKD [26].

More recently, the longitudinal prognostic value of ABPM in the AASK study was undertaken using baseline ABPM data and rate of CKD progression and subsequent CV outcomes were assessed [27••]. Participants were followed for a median of 5 years. Primary renal outcome was a composite of doubling of serum creatinine, ESRD, or death. The primary CV outcome was a composite of myocardial infarction, hospitalized congestive heart failure, stroke, revascularization procedures, CV death, and ESRD. Results showed that higher 24-h SBP, daytime, nighttime, and clinic SBP were each associated with subsequent renal (hazard ratio, 1.17–1.28; P<0.001) and CV outcomes (hazard ratio, 1.22–1.32; P<0.001). After controlling for clinic SBP, ABPM were predictive of renal outcomes in participants with clinic SBP<130 mmHg (P<0.05 for interaction). ABPM predicted CV outcomes with no interaction based on clinic BP control.

A recent study queried the role of the estimated glomerular filtration rate (eGFR) in the prediction of CV outcome over and beyond ABPM [28••]. This study was done in the general population. The authors assessed the health outcomes in 5,322 subjects (median age, 51.8 years; 43.1 % women) randomly recruited from 11 populations enrolled in the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) [29], who had baseline measurements of 24-h ABPM and eGFR. The population included 3,709 Europeans (69.7 %), 531 Asians (10.0 %), and 1,082 South Americans (20.3 %). Hypertension was present in 2,239, of whom 1,035 (46.3 %) were taking BP lowering drugs. Conventional BP averaged 131±21 / 80±11 mmHg. 24-h ABPM was 123±14 / 74±8 mmHg and mean serum creatinine was 0.99±0.17 mg/dL, and mean eGFR 79.4± 16.7 mL/min/1.73 m^2. Stage 3 CKD was present in 11 % of subjects. eGFR was 45 to 60 mL/min/1.73 m^2 in 552 participants (10.4 %) and 30 to 45 mL/min/1.73 m^2 in 58 (1.1 %). Among the 2,962 participants, who underwent testing for proteinuria, 67 had a positive dipstick test (any degree of proteinuria) and 179 had an albumin excretion of≥ 30 mg/day. The number of participants with more severe proteinuria on dipstick testing or having a 24-h albuminuria in excess of 300 mg amounted to only 77 and 2, respectively. Median follow-up was 9.3 years. Hazard ratios were computed using multivariable-adjusted Cox regression. ABPM predicted (P≤

0.008) both total (513 deaths) and CV (206) mortality whereas eGFR only predicted CV mortality (P=0.012). Furthermore, ABPM predicted ($P \leq 0.0056$) fatal combined with nonfatal events as a result of all CV causes (555 events), cardiac disease (335 events), or stroke (218 events), whereas eGFR only predicted the composite CV end point and stroke ($P \leq$ 0.035). For CV mortality, the composite CV end point, and stroke, ABPM added 0.35 %, 1.17 %, and 1.00 % to the risk already explained by cohort, sex, age, body mass index, smoking and drinking, previous CV disease, diabetes mellitus, and antihypertensive drug treatment. Adding eGFR explained an additional 0.13 %, 0.09 %, and 0.14 %, respectively. Sensitivity analyses stratified for ethnicity, sex, and the presence of hypertension or CKD (eGFR <60 mL/min/1.73 m^2) were confirmatory. The study demonstrates that in the general population, eGFR predicts fewer end points than ABPM, thus, ABPM is additive and adds prognostic value for predicting CKD and CV outcomes.

A prior observational study of ABPM in CKD was less suggestive of an association with CV outcomes when additional risk factors other than BP were considered. This study, conducted in 217 US Veterans with CKD followed for a median of 3.4 years, noted that after adjustment for clinic BP, the 24-h ambulatory systolic BP did predict a composite CV outcome of stoke, myocardial infarction, and death [30]. The composite outcome occurred in 57 of the participants (27 %). Each one standard deviation (SD) increase in systolic BP increased the hazard ratio (HR) of the CV end point by 1.66 [95 % CI 1.27–2.17] for BP measured at home, and 1.42 [95 % CI 1.10– 1.84] for BP measured over 24 hours. The SD for the home systolic BP was 21.4 mmHg and for ABPM it was 16.6 mmHg. The investigators observed that when a subjects BP was classified as controlled or increased by the specific monitoring technique (clinic, home or ABPM), only the 24-h ABPM was predictive of CV outcomes, whereas neither clinic nor home monitoring were predictive. With ABPM, the day and the night BP values were similar in predicting outcomes; nocturnal dipping did not appear to be of diagnostic importance in this study. When the investigators further adjusted the ABPM data for other CV risk factors using propensity score analysis, CV outcomes were not independently associated with 24-h ABPM.

In a randomized open-label clinical trial of timing of antihypertensive drug therapy in CKD, a study from Spain randomly assigned 332 patients with CKD to the usual morning dosing of BP medications, and 329 patients were assigned to take at least one antihypertensive medication at night [31]. In this study, ABPM was conducted for 48 hours. The outcome in this study was a complicated CV composite of death, myocardial infarction, angina pectoris, revascularization, heart failure, arterial occlusion of lower extremities, occlusion of the retinal artery, and stroke. After a mean follow-up of 5.4 years, there were 139 events (20.7 %). More than half of the subjects in each group of this study had an eGFR> 60 mL/min/1.73 m^2, and were diagnosed with CKD on the basis of albuminuria. The investigators observed lowered CV event rates in those randomized to nighttime dosing. Those randomized to at least one antihypertensive at night had lower nighttime BP compared with the conventional dosed group. The investigators observed that there was a J-shaped effect of clinic systolic BP with outcomes, but no such relationship was evident with pooling the study population and evaluating achieved nocturnal systolic BP levels.

To determine if ABPM could be used to adjust therapy in hypertensive children with CKD, the "Effect of Strict Blood Pressure Control and ACE Inhibition on CKD Progression in Pediatric Nephropathies (ESCAPE)" trial was undertaken [32•]. This trial showed that by intensifying BP control as assessed using ABPM with target 24-hour blood-pressure levels in the low range of normal, a substantial benefit with respect to renal function was seen among children with CKD. The causes of CKD in children are very different than those in the adult CKD population; however, ABPM is more cost effective than dialysis and transplantation, and worthwhile to consider if it influences treatment decisions in patients with established CKD and could potentially impact future CV and renal outcomes. The advantages of ABPM in CKD are summarized in Table 2.

Table 2 Advantages of ambulatory blood pressure monitoring (ABPM) in chronic kidney disease (CKD)

General Advantages of ABPM:
• Provides multiple readings compared with a typical office visit
• Captures the pattern of BP over a full daily cycle
• Provides information about night time dipping and reverse dipping status
• Identifies patients with white coat hypertension, which carries less risk than sustained hypertension
• Identifies patients with masked hypertension, which carries more risk than normotension
Advantages of ABPM specific to CKD:
• Better tool for predicting renal and CV risk than office BP
• Better tool for predicting CKD progression, ESRD or death than office BP
• ABPM is additive and adds prognostic value for predicting CKD and CV outcomes

BP blood pressure; *CV* cardiovascular; *ESRD* end stage renal disease

Conclusion

There are several reasons why ABPM provides greater opportunity to profile CV risk and renal disease progression in patients with CKD. It provides many more readings, often more than 50 measurements, compared with a typical office visit of three readings [33]. It captures the pattern of BP over a full daily cycle and cues the provider into the success, or failure, of BP suppression during the night [13]. By virtue of the large number of readings, it provides the opportunity to evaluate the variability of BP and heart rate, which have opposing effects on CV outcomes [34]. Finally, ABPM has shown that some patients 1) have higher in-office BP values compared with the rest of their day (white coat effect), which carries less risk than sustained hypertension (office and out-of-office readings both elevated); and 2) have higher out-of-office BP values compared with office BP values (masked hypertension effect), which carries more risk than normotension (office and out-of-office readings both controlled) [35]. The CRIC study [36] will provide more insight into the role of ABPM in CKD patients, as it has more than 1,500 participants studied with a focus on both CKD progression and CVD outcomes (Paul Drawz, Personal Communication).

Conflict of Interest Debbie L. Cohen declares that she has no conflict of interest.

Yonghong Huan declares that he has no conflict of interest.

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- • Of importance
- •• Of major importance

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