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Ambulatory blood pressure and cardiovascular events in chronic kidney disease

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Abstract

Purpose of review—Hypertension is an important risk factor for adverse cardiovascular and renal outcomes particularly in patients with chronic kidney disease. This review compares blood pressure measurements obtained in the clinic with those obtained outside the clinic to predict cardiovascular and renal injury and outcomes.

Recent findings—Data are accumulating that suggest that ambulatory blood pressure monitoring is a superior prognostic marker compared to blood pressures obtained in the clinic. Use of ambulatory blood pressure monitoring can detect white coat hypertension and masked hypertension which results in less misclassification of blood pressures. Ambulatory blood pressure monitoring is a marker of cardiovascular end points in CKD. Non dipping is associated with proteinuria and lower GFR. Although non-dipping is associated with more ESRD and cardiovascular events, adjustment for other risk factors removes the prognostic significance of non-dipping. For patients with CKD, not on dialysis, 24 hour ambulatory BP of <125/75 mm Hg, daytime ambulatory of <130/85 mm Hg and nighttime ambulatory BP of <110/70 mm Hg appear to be reasonable goal BP targets. In the management of hypertension in patients with CKD, control of hypertension is important. Ambulatory BP monitoring may be useful to assign more aggressive treatment to patients with masked hypertension and withdraw antihypertensive therapy in patients with white-coat hypertension.

Summary—Ambulatory blood pressure monitoring can refine cardiovascular and renal risk assessment in all stages of chronic kidney disease. The independent prognostic role of non-dipping is unclear.

Keywords

ambulatory blood pressure monitoring; cardiovascular disease; chronic kidney disease; home blood pressure monitoring; hypertension

Introduction

Hypertension is strong, modifiable, cardiovascular risk factor. Nearly all clinical decisions in hypertension are made using clinic blood pressure recordings, since the vast majority of cardiovascular risk assessment and antihypertensive trials was made using these measurements. However, blood pressure measurements can be obtained in the clinic, by self measurement at home and by automated ambulatory blood pressure recordings [1]. These

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recording methods have led to the recognition of hypertension that depends on the environment in which the blood pressure measurements are made. White coat hypertension and masked hypertension are two types of situational hypertension. White coat hypertension is defined as high blood pressure in the clinic and normal blood pressure by ambulatory blood pressure monitoring, whereas masked hypertension is normal blood pressure in the clinic and but higher blood pressure at home [2;3]. These measurements are more than statistical curiosities, since patients with white coat hypertension have a relatively benign prognosis. In contrast those with masked hypertension have increased cardiovascular events compared to those with persistent normotension. The purpose of this review is to evaluate the relationship of cardiovascular events with ambulatory blood pressure recordings in patients with chronic kidney disease.

Hypertension has a strong, graded and linear relationship with cardiovascular outcomes. In the million people meta-analysis the blood pressure associated with least cardiovascular risk, even among the very old, was 115/75 mm Hg. [4]. A single blood pressure of 110/70 mmHg, or usual blood pressure of 115/75 mmHg, has the lowest vascular mortality risk even among octogenarians, and there was no evidence for a J-curve in this population [4]. Thus optimal blood pressure is defined as <120/80 mm Hg. Prehypertension is defined as 120-139/80-89 mm Hg and hypertension 140/90 mm Hg or more [5]. In patients with diabetes mellitus or those with chronic kidney disease, the cardiovascular risk is increased to a substantial level at BP of 130/80 mm Hg therefore patients with these conditions are considered hypertensive at 130/80 mm Hg [5]. What is evident from above is the inherent relationship of a given level of blood pressure and cardiovascular event rate. Thus, in higher risk patients, a lower blood pressure confers a greater cardiovascular risk compared to higher blood pressure.

Blood pressure misclassification in Chronic Kidney Disease

Hypertension control rates among patients with chronic kidney disease (CKD) are dismal. The control rates of hypertension depend on the technique of BP measurement. Among patients with CKD, although 75% were treated with blood pressure medications, 14% reached the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) VI goal of lower than 130/85 mmHg, and 36% reached a goal of lower than 140/90 mmHg when blood pressures were obtained in the clinic. Overall, 11% with CKD reached the JNC VI goal (<130/85 mmHg) and 27% reached 140/90 mmHg [6].

To illustrate the notion that blood pressure control rates depend on how blood pressure is measured consider a study done in 232 patients (20% Black, 4% females, mean age 67 yrs, 35% diabetics) with chronic kidney disease underwent a single 24-hour ambulatory blood pressure monitoring and concomitant recording of BP in the clinic and at home for one week [7]. Hypertension was defined as systolic BP $\geq$ 130 mm Hg or diastolic BP $\geq$ 80 mm Hg on average awake 24-hour ambulatory blood pressure monitoring. In this sample of Veterans with CKD, systolic hypertension—with or without concomitant diastolic hypertension—was seen in 62% of the patients whereas isolated diastolic hypertension was seen in only 3%. The low prevalence of isolated diastolic hypertension is what has been reported previously in hemodialysis patients [8]. Whereas 70% of patients had diastolic BP within recommended levels only 38% had well controlled systolic BP when judged by ambulatory BP monitoring. Therefore attention should be focused on control of systolic BP in patients with CKD. Adequate systolic BP control (<130 mm Hg) was seen in 19-28% of CKD patients when clinic blood pressures were used to assess control. However, using ambulatory blood pressure monitoring, blood pressure control was seen in 38% (which is still dismal).

The phenomenon of white-coat hypertension is reported in 20-35% of patients with essential hypertension [5], is more pronounced when blood pressure is measured by a physician than by

a technician [9], and less prevalent in those with coexisting target organ damage is present [10]. Clinic blood pressures—even when obtained by standardized technique—were misleading in a large proportion of patients with CKD. In these patients there was a high prevalence (28-30%) of white coat effect when assessed by clinic systolic BP but a little less (24%) when assessed by systolic home blood pressure monitoring. The Seventh Joint National Committee recommends the use of home BP monitoring before considering ambulatory BP monitoring to assess the value of clinic blood pressures [5]. The goal of home BP monitoring would be to reduce the white-coat effect. We found that the white-coat effect is at least as common in patients with CKD as those with essential hypertension and the white-coat effect is not significantly attenuated even with home BP monitoring.

More importantly, in 26-34% of CKD patients clinic systolic BP were found to be normal but ambulatory BP found to be hypertensive, what has been called masked hypertension. In contrast, if systolic BP was found to be normal at home, only 13% were found to be hypertensive by ambulatory BP. Bobrie et al have reported that in elderly patients with masked essential hypertension, cardiovascular event rate is similar to that found in the hypertensive population [11]. If these results are extrapolated to patients with CKD, it would be important to identify and treat as many as a third of patients with have masked hypertension by clinic BP measurements. The prognostic impact of these findings is discussed in the subsequent sections.

Ambulatory blood pressure monitoring and ESRD outcomes in CKD

Timio et al performed a three-year longitudinal case-control study in 48 hypertensives with CKD divided into dippers (n=20) and non-dippers (n=28) [12]. They were among the first to report that non-dippers had a faster rate of fall in creatinine clearance than the dippers (0.37 ± 0.26 vs 0.27 ± 0.09 ml/min/month; $p = 0.002$). The non-dippers also had greater increase in urinary protein excretion rate than dippers (993 ± 438 vs 691 ± 222 mg/24 h; $p = 0.009$). This longitudinal study suggests that the non-dipping pattern of ambulatory BP can be associated with a faster progression of CKD. However, hard outcomes were not measured and the study had small number of subjects.

To test the utility of ambulatory BP monitoring over clinic BP monitoring to predict renal outcomes, Agarwal et al performed a longitudinal cohort study of 217 Veterans with CKD [13]. 24-hour ambulatory BP was $133.5 \pm 16.6/73.1 \pm 11.1$ mm Hg and clinic BP was $155.2 \pm 25.6/84.7 \pm 14.2$ mm Hg. The composite renal end-point of ESRD or death over a median follow up of 3.5 years occurred in 75 patients (34.5%), death occurred in 52 patients (24.0%) and ESRD in 36/178 patients (20.2%). 39 patients died before reaching ESRD. Ambulatory BP appeared to provide greater prognostic information compared to clinic blood pressure. One standard deviation (SD) increase in systolic BP increased the risk of composite outcome 1.69 (95% confidence interval [CI] 1.32 - 2.17) for standard clinic measurement, and 1.88 (95% CI 1.48 - 2.39) for 24 hour ambulatory BP recording. The results of this prospective cohort study demonstrated that, after adjustment for clinic blood pressure, 24-hour ambulatory systolic blood pressure provided additional prognostic information concerning ESRD and the composite end point of ESRD and death. One SD increase in 24 hour ambulatory systolic BP increased the risk of ESRD 3.04 (95% CI 2.13 - 4.35) and 2.20 (95% CI 1.43 - 3.39) when adjusted for standard clinic systolic BP. Amongst the components of the end-points that were studied, the strongest relationship emerged between systolic blood pressure and ESRD, compared to all-cause mortality or the composite end-point. Whereas day ambulatory BP was a stronger predictor of ESRD, night ambulatory BP was a stronger predictor of total mortality and the composite renal end-point.

Dipping added to the prognostic importance of ambulatory BP monitoring in predicting ESRD or deaths in our study, even after adjusting for 24-hour ambulatory systolic BP. Dipping in

patients with CKD is associated with younger age, better GFR, lower proteinuria and higher serum albumin concentration [14]. These risk factors also are associated with progression of kidney disease. We found that adjustment for other risk factors for CKD progression removes the independent prognostic value of ambulatory BP. Thus, it is unclear whether non-dipping is an independent risk factor or simply a marker of more severe kidney disease.

In a retrospective cohort study of 322 patients with and without CKD, Davidson et al reported a greater decline in estimated GFR in nondippers compared to dippers during a median follow up of 3.2 years [15]. Mean change in 137 dippers in estimated GFR was 1.3% whereas the mean change in 185 nondippers was -15.9% ($p < 0.001$ for difference). The differences in GFR decline remained after adjusting for other risk factors. Notably, no information on proteinuria was provided. Since nondipping and CKD progression are both strongly linked to proteinuria, whether nondipping is truly an independent marker of progression remains open to question.

Ambulatory BP and Cardiovascular Outcomes in CKD

To assess the role of out-of-clinic BP recordings in predicting cardiovascular events in patients with chronic kidney disease (CKD) a prospective cohort study was conducted in 217 Veterans with CKD [16]. The cohort of patients had previously been reported for ESRD and mortality outcomes above [13]. The results of this prospective cohort study demonstrate that, after adjustment for clinic blood pressure, 24-hour ambulatory systolic blood pressure provided additional prognostic information concerning the composite cardiovascular end point of myocardial infarction, stroke and death. One SD increase in systolic BP increased the hazard ratio (HR) of composite end point by 1.16, (95% confidence interval [CI] 0.89 - 1.50), for routine BP, 1.57 (95% CI 1.19 - 2.09) for standardized BP, 1.66, (95% CI 1.27 - 2.17) for home BP and 1.42 (95% CI 1.10 - 1.84) for 24-hour ambulatory BP recording. The HR of composite end point was only significant for hypertension defined by 24 hour ambulatory BP monitoring (HR 2.22 (95% CI 1.23 - 4.01)). Only hypertension as defined by 24-hour ambulatory BP was predictive of cardiovascular outcomes, whereas definitions based on clinic or home monitoring were not. Awake and asleep BP were similar in predicting outcomes and dipping did not add to the diagnostic importance of ambulatory BP monitoring our study. Non-dipping was associated with increased cardiovascular risk, but not when adjusted for other risk factors. When adjusted for risk factors for cardiovascular outcomes (by propensity score analysis), even 24-hour ambulatory BP monitoring was not independently associated with cardiovascular outcomes. Thus, factors that elevate blood pressure such as severity of kidney disease may mediate the risk that is measured through blood pressure.

Several investigators have reported the cardiovascular risk associated with ambulatory blood pressure monitoring in patients with ESRD. For example, in 80 patients on chronic hemodialysis, In 80 patients on chronic hemodialysis, Liu et al have shown that non-dipping was associated with a hazard ratio of 2.5 for cardiovascular events and 9.6 for cardiovascular death [17]. Tripepi et al have shown that in hemodialysis patients without diabetes mellitus and cardiovascular events, the night/day ratio is a predictor of total mortality and cardiovascular mortality [18]. Interestingly, we found day blood pressure to be a stronger predictor of ESRD while the night systolic blood pressure to be a stronger predictor of deaths. Amar et al, reported that nocturnal blood pressure was linked to mortality in French hemodialysis patients [19].

Ambulatory blood pressure monitoring requires inflation of an arm cuff at pre-specified intervals to obtain a blood pressure recording, which can disturb sleep. If sleep is disturbed then dipping may not be seen. Verdecchia et al asked their patients if perceived sleep was disturbed during BP monitoring [20]. They report that if sleep is disturbed due to ambulatory blood pressure monitoring, then dipping (or lack thereof) was of no prognostic significance. On the other hand, if dipping is absent and the patient slept well, it was of prognostic

importance. Although the results of this study may be explained by interference with sleep, it is also possible that many of the patients who reported lack of sleep were those with CKD. Nocturia (and hence disturbed sleep) is an early feature of CKD. Previous studies have demonstrated that not dipping is associated with greater proteinuria and lower GFR. Thus, these factors which modulate events instead of presumed lack of sleep. Nonetheless, it would be prudent to ask subjects about the quality of sleep during ambulatory blood pressure monitoring and also adjust the analyses for proteinuria and GFR in epidemiological studies.

What is goal ambulatory blood pressure in CKD?

To calibrate the blood pressure level using ambulatory blood pressure monitoring that is associated with optimal, normal or hypertensive clinic blood pressure an international collaboration of investigators led to analysis of pooled data in normal individuals and patients with essential hypertension in several countries [21]. The investigators found that the level of 24-hour ambulatory blood pressure associated with cardiovascular mortality rate similar to hypertensive blood pressure ($>140/90$ mm Hg) was $130/80$ mm Hg. Thresholds for optimal ambulatory BP was $115/75$ mm Hg for 24 hours, $120/80$ mm Hg for daytime, and $100/65$ mm Hg for nighttime. Rounded thresholds for normal ambulatory BP were $125/75$, $130/85$, and $110/70$ mm Hg, respectively, and those for ambulatory hypertension were $130/80$, $140/85$, and $120/70$ mm Hg. The definition of hypertension in the current AHA guideline is awake ambulatory BP of $>135/85$ mm Hg. Thus, the definitions of ambulatory blood pressure are evolving.

The level of goal ambulatory blood pressure in patients with CKD is unknown. Since the goal BP for CKD is taken to be $<130/80$ mm Hg which is considered normal BP, 24 hour ambulatory BP of $<125/75$ mm Hg, daytime ambulatory of $<130/85$ mm Hg and nighttime ambulatory BP of $<110/70$ mm Hg would be considered reasonable goal BP targets. In patients on dialysis, it is even harder to speculate the goal ambulatory BP. However, the thresholds may be higher: $<130/80$ for 24 hours, $<140/85$ mm hg for daytime and $<120/70$ mm Hg nighttime.

Conclusion

Ambulatory blood pressure monitoring appears to be a superior prognostic marker compared to blood pressures obtained in the clinic. Use of ambulatory blood pressure monitoring results in less misclassification of blood pressures. Thus, ambulatory blood pressure monitoring can identify white coat hypertension and masked hypertension. The latter is associated with higher risk of end-stage renal disease in patients with chronic kidney disease. Ambulatory blood pressure monitoring is a marker of cardiovascular end points in CKD. Non dipping is associated with proteinuria and lower GFR. Although non-dipping is associated with more ESRD and cardiovascular events, adjustment for other risk factors removes the prognostic significance of non-dipping. Thus, it is unclear whether non-dipping is of independent prognostic significance. For patients with CKD, not on dialysis, it appears that 24 hour ambulatory BP of $<125/75$ mm Hg, daytime ambulatory of $<130/85$ mm Hg and nighttime ambulatory BP of $<110/70$ mm Hg would be considered reasonable goal BP targets.

In the management of hypertension in patients with CKD, control of hypertension is important. Ambulatory BP monitoring may be useful to assign more aggressive treatment to patients with masked hypertension and withdraw antihypertensive therapy in patients with white-coat hypertension.

Abbreviations

CKD, chronic kidney disease; ESRD, end-stage renal disease.

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Figure 1. Cumulative risk of end-stage renal disease (ESRD) according to level of systolic ambulatory blood pressure (BP)

24-hour ambulatory systolic blood pressures were divided into three categories, <130 mm Hg, $130\text{--}<160$ mm Hg and ≥ 160 mm Hg or more, reflecting nationally recommended levels of control, and two degrees of poor control. 3/76 (4%) patients in the well controlled category had ESRD, 23/88 (26%) patients in $130\text{--}<160$ mm Hg had ESRD and 8/11 (73%) in the ≥ 160 mm Hg or more category had ESRD ($p<0.0001$ by log-rank test). (From Agarwal R, Andersen MJ: Kidney Int. 2006, 69:1175-1180. with permission)