Hypertension in Chronic Kidney Disease Part 2
Role of Ambulatory and Home Blood Pressure Monitoring for Assessing Alterations in Blood Pressure Variability and Blood Pressure Profiles

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Blood pressure (BP) is characterized by high variability, including changes beat-to-beat (very short term), within 24 hours (short term), from day to day (midterm), and between visits spaced by weeks, months, seasons, and even years (long term). These variations can be estimated by means of continuous beat-to-beat BP recordings, repeated conventional office BP measures, 24-hour ambulatory BP monitoring (ABPM), or home BP monitoring (HBPM) over longer time windows (Table). A main advantage of ABPM over other BP measurement techniques is represented by its ability to track BP changes occurring in daily life conditions and during 24 hours, thus allowing assessment of overall BP variability (BPV) as well as identification of its specific components, such as nocturnal hypertension and altered day-to-night BP profiles (ie, morning BP rise, nondipping pattern of BP) which become manifest early in the course of chronic kidney disease (CKD). These alterations are even more significant in subjects with end-stage renal disease (ESRD) mainly, but not exclusively, because of the marked reduction in intravascular volume immediately after hemodialysis followed by the progressive increase in volemia throughout the interdiagnostic period, combined with an enhanced sympathetic activity. The higher frequency of alterations in 24-hour BP profiles and BPV in subjects with CKD and in those with ESRD not only makes a proper assessment and achievement of BP control more difficult in these subjects but may be prognostically relevant on the background of the evidence from longitudinal and observational studies indicating that increased BPV may predict the development of cardiovascular and renal disease, over and above the contribution of elevated mean BP levels per se. The purpose of this review is to address the currently available evidence on the role of ABPM and HBPM for the assessment and management of alterations in circadian BP profiles and in BPV in patients with CKD.

Mechanisms of BPV
In physiological conditions, BP fluctuations occurring on a beat-by-beat basis and within the 24 hours may represent a homeostatic response of neural (ie, central sympathetic drive and its reflex modulation by arterial and cardiopulmonary reflexes), humoral (catecholamines, insulin, angiotensin II, bradykinin, endothelin-1, and nitric oxide), vascular (ie, elastic properties of arteries), and rheological mechanisms (ie, blood viscosity) to environmental (weather changes), behavioral (ie, physical activity, sleep, postural changes), and emotional (ie, psychological stress) stimuli. In particular conditions, such as...
as CKD, sustained increases in short-term BP may reflect important alterations in regulatory mechanisms (ie, enhanced sympathetic drive and impaired baroreflex function) which may themselves also promote alterations in the cardiovascular system, directly affecting organ damage, such as left ventricular hypertrophy, and cardiovascular events. Although the mechanisms influencing day-by-day BP fluctuations still need to be better understood, evidence has been provided that behavioral factors may importantly influence midterm BPV as indicated by the significant changes in ambulatory BP levels between working days and the weekend.1 Regarding long-term BPV, several clinical trials in hypertension have suggested that it may be importantly affected by treatment-related factors leading to inconsistent BP control (related to poor patient’s adherence to prescribed drugs, improper dosing/titration of antihypertensive treatment, dose omission, or delay in drug intake during the follow-up period), but also errors in BP measurement may importantly influence BP variations from visit-to-visit.1

Finally, in ESRD patients, who have lost their residual renal function, the significant shifts in electrolyte and the intravascular volume (ie, marked reductions immediately after hemodialysis and then progressive increases throughout the interdialytic period), may determine a highly variable and more complex behavior of BP (either over the 24-hour period or from day-to-night and day-to-day). Indeed, extensive studies in ESRD over the past decade have indicated that plasma volume changes are the major determinants of BPV and that volume overload relates to hypertension resistance in these patients.62–65 The occurrence of BP fluctuations shifting from a daily cycle to a cycle every 2 to 3 days, in relation to ultrafiltration and interdialytic fluid gain, introduces a much more complex pattern of variability in hemodialysis patients. Other factors influencing BP regulation in ESRD include alterations in cardiac function (cardiac output), an increased large artery stiffness and pulse wave reflections, prescription of postdialysis target weight, sodium load, administration of erythropoiesis-stimulating agents, the type and timing of administration of antihypertensive drugs, and dialysate composition.

### ABPM in the Assessment of Short-Term BPV and Its Clinical Implications

Although an accurate assessment of the fast and short-lasting changes in BP levels requires the use of continuous beat-to-beat BP recordings, this may at least in part be possible also through use of noninvasive ABPM with measurements at intervals from 15 to 20 minutes.66,67 Intermittent BP measurements collected with ABPM allow the estimation of short-term BPV by calculating 24-hour BP standard deviation (SD),66 and also to account for its dependence on mean BP levels, by calculating the coefficient of variation (SD×100/BP mean).66 As calculation of 24-hour SD is significantly influenced not only by fast BP fluctuations, which may have a negative impact on prognosis, but also by nighttime BP dipping (ie, an index of BPV with favorable prognostic implications), several indices have been proposed to estimate short-term BP changes throughout the 24 hours without the confounding effects of day-night BP fluctuations. These indices include (1) weighted

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**Table. Different Components of BPV and Methods for Their Measurement**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Very Short-Term BPV (Beat-by-Beat)</th>
<th>Short-Term BPV (Within 24 h)</th>
<th>Midterm BPV (Day-by-Day)</th>
<th>Long-Term BPV (Visit-to-Visit)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Method for BP measurement</strong></td>
<td>Continuous BP recordings in a laboratory setting or under ambulatory conditions</td>
<td>ABPM</td>
<td>ABPM over ≥48 h, HBPM</td>
<td>OBP, ABPM, HBPM</td>
</tr>
<tr>
<td><strong>Measurement intervals</strong></td>
<td>Beat-to-beat over variable recording periods (1 min to 24 h)</td>
<td>Every 15–20 min for 24 h</td>
<td>Day-by-day, over several days, weeks, or months</td>
<td>Spaced by visit over weeks, months, and years</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Assessment of indices of autonomic cardiovascular modulation</td>
<td>Extensive information on 24-hour BP profile Identification of patterns of circadian BP variation Evaluation of effects of daily life stress</td>
<td>Appropriate for long-term monitoring Assessment of consistency of BP control by treatment</td>
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</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Stability of measurements might not be guaranteed outside the laboratory setting</td>
<td>Cannot be repeated frequently</td>
<td>Patient training and involvement is required for HBPM ABPM for 48 h is not always well tolerated nor well accepted by patients</td>
<td>OBP and HBPM provide limited information on BP profiles</td>
</tr>
<tr>
<td><strong>Indices of BPV</strong></td>
<td>SD, CV</td>
<td>24-h, day- and nighttime SD and CV 24-h weighted SD Day-to-night BP changes ARV Residual short-term components assessed by spectral analysis</td>
<td>SD, CV</td>
<td>SD, CV, VIM</td>
</tr>
</tbody>
</table>

ABPM indicates ambulatory blood pressure monitoring; ARV, average real variability; BP, blood pressure; BPV, blood pressure variability; CV, coefficient of variation; HBPM, home blood pressure monitoring; OBP, office blood pressure; SD, standard deviation; and VM, variation independent of mean. Modified from Parati et al1 with permission of the publisher. Copyright © 2013, Nature Publishing Group.
24-hour BP SD, computed as the average of daytime and nighttime BP SD, each weighted for the duration of the day and nighttime periods, respectively; (2) residual BPV, calculated through spectral analysis by considering the spectral power of faster BP fluctuations remaining in the 24-hour tracing after exclusion of slower components of 24-hour BP fluctuations (ie, day-night and siesta-related postprandial BP changes); (3) the average real variability, computed as the average of the absolute differences between consecutive BP measurements during 24 hours. From a prognostic perspective, assessment of these indices may be relevant on the background of the evidence supporting the association between increasing values of short-term BPV within 24 hours and an increased prevalence and progression of cardiac, vascular, and renal subclinical organ damage; ‡BPV on a beat-by-beat basis has not been routinely measured in population studies. AHT indicates antihypertensive treatment; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IHD, ischemic heart disease; MA, microalbuminuria; MI, myocardial infarction; and SOD, subclinical organ damage. References supporting the association of BPV with cardiovascular and renal outcomes: short-term BPV: 3–39; midterm BPV: 9–11, 40–58; long-term BPV: 51, 59–61. Reprinted from Parati et al† with permission of the publisher. Copyright © 2013, Nature Publishing Group.

**Figure 1.** Different types of blood pressure variability (BPV), their determinants, and prognostic relevance for cardiovascular and renal outcomes. *Distinction between long-term (<5 years) and very long–term (≥5 years) BPV as proposed by Hastie et al.††Cardiac, vascular, and renal subclinical organ damage; ‡BPV on a beat-by-beat basis has not been routinely measured in population studies. AHT indicates antihypertensive treatment; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IHD, ischemic heart disease; MA, microalbuminuria; MI, myocardial infarction; and SOD, subclinical organ damage. References supporting the association of BPV with cardiovascular and renal outcomes: short-term BPV: 3–39; midterm BPV: 9–11, 40–58; long-term BPV: 51, 59–61. Reprinted from Parati et al† with permission of the publisher. Copyright © 2013, Nature Publishing Group.

ABPM in the Assessment of Night Hypertension, Altered Day-Night BP Profiles, and Their Clinical Implications

A major advantage of 24-hour ABPM over other BP measuring techniques is the possibility to assess BP levels both during daytime activity and nighttime sleep. By analyzing the changes in BP levels from day-to-night, it is indeed possible to identify individuals with a blunted nocturnal BP dipping (ie, nondippers, with a fall in nighttime systolic and diastolic BP<10% of daytime BP) or those who present an
increase rather than a decrease in nocturnal BP (so called risers or inverted dippers).23 Remarkably, a nondipping profile of BP is frequently accompanied by increased nocturnal mean BP levels (ie, nighttime BP>125/70 mmHg).24 This is relevant, if one considers that compared with normotensive and hypertensive subjects without CKD, patients with CKD often show marked alterations, disappearance (nondipping), or even inversion (reverse dipping) of the circadian BP variation. Loss of the normal nocturnal decline in BP is present in ≈50% of CKD patients and its frequency increases as renal dysfunction progresses, affecting up to 80% of patients who have reached ESRD.22 The prevalence of the rising BP pattern, which has been associated with a high cardiovascular risk in hypertensive patients without CKD, may be up to 2.5-fold more prevalent in CKD, and up to 5-fold more prevalent in ESRD.26 Potential mechanisms for these alterations in CKD patients include an increase in sympathetic drive during nighttime,77 enhanced salt sensitivity because of a reduced sodium excretory ability,78,79 sleep breathing disorders (ie, obstructive sleep apnea), leptin and insulin resistance,80 endothelial dysfunction,81 and glucocorticoid, 82,83 or cyclosporine use.84 Longitudinal studies in CKD populations have provided evidence that elevated nighttime BP levels are better predictors of fatal and nonfatal cardiovascular events, progression to ESRD, and mortality than daytime or 24-hour BP levels.23,24,45–87 It has also been shown that independently of other components of ABPM, average nighttime BP is an independent predictor of development and progression of microalbuminuria and reductions in glomerular filtration rate.25,26,88,89 up to progression to ESRD requiring dialysis.23,85 The clinical importance of a nondipping BP pattern has been first suggested by longitudinal studies in non-CKD patients, in which a nondipping and a reverse dipping pattern of nighttime BP was an independent predictor of development and progression of microalbuminuria,24–26 an increase in proteinuria,30 reductions in glomerular filtration rate, and increase in creatinine levels.22,31–34 In CKD patients, faster deterioration of renal function and progression to ESRD have been reported to be associated with BP nondipping at night (Figure 2). Several studies in CKD populations have indeed provided evidence that nondipping pattern of BP is associated with an increased risk of ESRD and all-cause mortality30 and with the combined end point of all-cause mortality, myocardial infarction, or stroke.23,24,37 In particular, one of these studies indicated that night/day BP ratio is an important predictor of cardiovascular outcome over and above the risk conferred by left ventricular hypertrophy (Figure 3).

**Chronotherapy of Hypertension in Patients With CKD**

Overall, the data provided by prospective studies in CKD support the prognostic relevance of identifying altered day-to-night BP profiles and suggest the possible importance of targeting BP-lowering strategies to its normalization. Because insufficient BP control at night is often caused by low blood drug concentrations, ABPM might be particularly useful to identify the optimal time of dosing for antihypertensive medications to normalize alterations in circadian BP profiles. Possible suggestions may include taking drugs once daily before going to bed in cases of isolated nighttime hypertension, or taking drugs whose effects are spread over the day in case of daytime hypertension, or, finally, using long-acting antihypertensive drugs when both day- and nighttime BP levels are elevated. Indeed, a prospective study in non-CKD patients showed that decreasing BP during sleep may confer substantial reductions in the incidence of cardiovascular events and mortality, independently of changes in any other ABPM variables.26 A recent study in nondipping subjects with CKD showed the effectiveness of shifting the administration of antihypertensive drugs from morning to evening in restoring BP dipping as well as in decreasing nocturnal BP and in reducing proteinuria while avoiding intensification of the required therapy.26 Another report also showed that administration of ≥2 medications at bedtime in CKD patients was significantly associated with lower systolic and diastolic BP mean levels during sleep than treatment with all medications on awakening and with higher rates of ambulatory BP control.30 Finally, because volume overload may selectively increase nighttime BP via mechanisms similar to those implicated in salt-sensitive hypertension, several studies implementing salt restriction or diuretic treatment/potassium supplementation in nondipper subjects with hypertension and CKD, have found these strategies effective in restoring normal BP dipping.82,93 Despite all the above evidence, it should still be better clarified by randomized intervention trials whether selective reduction of nocturnal BP or changing a patient from being a nondipper to dipper can be a therapeutic target aimed at reducing cardiovascular risk and at preventing CKD progression.

**Midterm BPV (Day-by-Day Assessment by HBPM), Long-Term (Visit-to-Visit) BPV, and Their Clinical Implications**

Although an accurate quantification of midterm BPV (ie, BP variations occurring on a day-by-day basis) could theoretically be obtained by performing ABPM recordings over 48 hours or more, duplicated ABPM is neither always feasible nor tolerated or accepted by patients, in particular by CKD patients.
and even less so by patients with ESRD on hemodialysis. The most practical approach for assessing day-by-day BPV thus consists in calculating BPV from self BP measurements obtained at home over several days under daily life conditions (Table). Indeed HBPM and ABPM provide complementary rather than overlapping information. Although HBPM may not provide the same detailed information on 24-hour BP behavior as ABPM does, it offers the possibility to estimate the behavior of BP over subsequent days, weeks, or months. Repeated assessment of home BP values, averaged 1 week before each visit to the doctor, may as well offer a solid base to assess BPV in the long-term follow-up (ie, visit-to-visit BPV), while allowing assessment of the consistency in BP control over time, an assessment that could be obtained also by analyzing CBP values obtained over repeated visits. From a prognostic perspective, consistent evidence has been provided in non-CKD populations that day-by-day home BPV may add to cardiovascular prediction over and above average home BP. Increasing values of day-by-day BPV have been associated with a higher prevalence and severity of target organ damage (ie, increased left ventricular mass index, carotid intima-media thickness, or urinary albumin:creatinine ratio) and with fatal and nonfatal cardiovascular events. Evidence has also been provided that increasing values of visit-to-visit BPV are significant predictors of cardiac (diastolic dysfunction), vascular (increased carotid intima-media thickness and stiffness), renal (development of micro- and macroalbuminuria and renal vascular atherosclerosis) organ damage, fatal, and nonfatal cardiovascular events and all-cause mortality independently of average BP values. A recent study in 48,587 Japanese subjects without diabetes mellitus or CKD found visit-to-visit BPV to be associated with new-onset CKD independently of average BP values and other clinical characteristics. Studies focusing on patients with type 1 diabetes mellitus have also indicated that increasing values of visit-to-visit BPV may be predictive of development and progression of renal damage (development/progression of albuminuria). Furthermore, in subjects with type 2 diabetes mellitus, increasing values of visit-to-visit BPV (as assessed through coefficient of variation) have been shown to be significantly correlated with urinary albumin excretion. Most importantly, in longitudinal studies increasing values of visit-to-visit BPV were predictive of the long-term development and progression of albuminuria independently of average BP levels and of the confounding effect of other cardiovascular risk factors. Based on these findings, some authors have proposed visit-to-visit BPV in systolic BP as a novel risk factor for progression of diabetic nephropathy or development of albuminuria in patients with type 2 diabetes mellitus. When focusing on CKD populations, whether or not with diabetes mellitus, several studies, but not all, have shown increasing values of day-by-day home BPV to be significant predictors of development and progression of nephropathy. Finally, in a recent retrospective analysis of a community-based cohort of 114,900 adults with CKD stages 3 to 4, increasing values of visit-to-visit BPV (defined as coefficient of variation, SD, or average real variability) were associated with higher risk of death, incident-treated ESRD, and cardiovascular events. A peculiar and specific form of midterm BPV, whose clinical implications are only partly understood, characterizes ESRD patients on hemodialysis. In these patients, BP is low throughout the day of dialysis but may display a different behavior during the interdialytic time period: in some patients it increases tremendously, whereas in others it is only moderately elevated. Little information is available on the impact of these different hemodialysis-related BPV patterns, which may lead to a different hemodynamic load on the cardiovascular system throughout the entire interdialytic time period. Another peculiar BPV pattern which can be observed in hemodialysis patients is the possible occurrence of intradialytic hypotension and intradialytic hypertension, whose impact on cardiovascular outcome would deserve to be explored by ad hoc longitudinal studies. The occurrence of these BP patterns in hemodialysis patients and the findings of studies focusing...
on mid- and long-term BPV in CKD patients have raised the question on whether antihypertensive treatment in subjects with CKD should be targeted also at normalizing alterations in mid-/long-term BPV in addition to achieving control of average BP values to improve cardiovascular and renal protection.

Previous studies in treated hypertensive patients without CKD seem to indirectly support this view. In the International Verapamil-Trandolapril (INVEST) study in treated hypertensives at high cardiovascular risk, progressive and significant reductions in the incidence of fatal and nonfatal cardiovascular events were reported to occur with the increase in the percentage of on-treatment visits with controlled BP (BP<140/90 mm Hg), even after adjustment for on-treatment reductions in average BP levels. These data seem to indirectly support the concept that a low visit-to-visit variability in BP may be associated with a better protection, and that achievement of a consistent BP control over time could be an additional target of antihypertensive treatment. In clinical practice, this objective could be more easily achieved by implementation of HBPM for assessing the rates and consistency of BP control over time. These results may be relevant also to the management of CKD patients, and in particular of patients with ESRD, in whom interdialytic weight gain may importantly modify BP levels, making out-of-office BP monitoring of crucial importance in achieving BP control.

In non-CKD populations also evidence that specific drug classes may improve cardiovascular outcome through their effects on long-term BPV has been provided by recent meta-analyses of clinical trials in hypertension, indicating that certain antihypertensive drugs may confer additional benefits on cardiovascular protection, because of their ability to reduce visit-to-visit BPV independently of their BP-lowering effects. Post hoc analyses of the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) and the Medical Research Council Trial of Treatment of Hypertension in Older Adults (MRC-elderly) showed that a treatment based on the calcium antagonist amlodipine was more effective in reducing intradividual visit-to-visit BPV and the incidence of stroke, than a treatment based on the β-blocker atenolol, independently of reductions in mean BP levels. On the other hand, a post hoc analysis of the European Lacidipine Study on Atherosclerosis (ELSA study) in mild-to-moderate hypertensives at low cardiovascular risk found no significant differences between calcium channel blockers and β-blockers in their ability to reduce visit-to-visit BPV.

We have to acknowledge that evidence on the importance of modulating mid- and long-term BPV by treatment in CKD or in ESRD patients is still missing, however, and longitudinal randomized intervention trials are needed in this regard.

Conclusions

Subjects with CKD, and in particular those on hemodialysis are characterized by marked hemodynamic changes and by a high prevalence of alterations in circadian BP profiles and increased values of BPV, which have been shown to be associated with adverse cardiovascular and renal prognosis over and above the contribution of elevated mean BP levels. Although ABPM allows assessment of alterations in day-night BP changes and short-term BPV, a proper implementation of HBPM offers the possibility to assess BP levels on a day-by-day basis and estimation of BPV in the mid/long term. Also an increase in midterm BPV as well as an increase in long-term visit-to-visit BPV was associated with adverse consequences in CKD patients. Such information might be useful to the practicing physician to optimize antihypertensive treatment, and to achieve long-term stable BP control. Some prospective studies in hypertension and in CKD have suggested the prognostic relevance of identifying altered day-to-night BP profiles and of targeting BP-lowering strategies to their normalization to reduce cardiovascular morbidity and mortality and to limit the progression of CKD. Despite the above data, however, more evidence is still needed to determine what the normal values of BPV and what the BPV targets to be achieved by treatment might be, and whether targeting antihypertensive treatment at normalizing alterations in day-night BP changes and at reducing short-, mid-, and long-term BPV may confer additional benefits in terms of cardiovascular and renal protection over and above the concomitant reductions in average BP levels. BPV should thus remain confined to a research setting until the above questions find a proper response in the context of randomized ad hoc intervention trials. These trials should test the hypothesis that patients who are randomized to adapt medication based on regular ABPM/HBPM measurements have better outcomes than those randomized to CBP measurements only, and should clarify whether treatment-induced reductions in BPV are or are not followed by a reduction in cardiovascular events rate and mortality.

Disclosures

None.

References


Blood Pressure Variability in Renal Disease

Parati et al


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