Invited Comment

Ambulatory blood pressure monitoring: an essential tool for blood pressure assessment in uraemic patients

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Keywords: ambulatory blood pressure monitoring; blood pressure circadian variability; diurnal blood pressure; non-dipping; uraemia

Introduction

Ambulatory blood pressure monitoring (ABPM) has been growing steadily in popularity, as equipment becomes more portable, accurate and affordable, software packages more powerful, and physicians more accepting of its advantages (see Table 1). However, the most recent guidelines from National and International Hypertension Societies only advocate its use in ‘difficult’ cases (Table 2) [1]. This conservatism sits uncomfortably alongside the repeated observation that up to one in four so-called hypertensive patients have normal ambulatory BP levels away from the clinical setting [2].

From the early use of direct intra-arterial blood pressure (BP) recordings, the beat-to-beat, minute-to-minute variability of BP has been appreciated [3]. Diurnal BP variation has been studied intensively for several decades. Diurnal BP normally falls with sleep; this behaviour is normally distributed in normotensive and hypertensive populations, and is attenuated with age [4]. The reasons for this change are obscure, both in essential and secondary hypertension, but in many studies BP values at night have a greater predictive power in terms of end-organ damage than daytime BP values [5–7].

Abnormality (reduction) in the fall in diurnal BP with sleep is observed consistently in patients with chronic renal diseases (for review see [8]). Important mechanisms to explain these changes include autonomic dysfunction and obstructive sleep apnoea (see [9,10]). Although volume status and relative hydration status are also believed by some to be relevant, the recent elegant intra-institutional trial by the Perugia group examining the benefits of short-hours daily haemodialysis clearly showed greatly reduced BP, reduced left ventricular mass and reduced volume expansion in those patients undergoing daily haemodialysis compared with thrice-weekly conventional haemodialysis. However, the diurnal BP rhythm was not improved; thus, in dialysis patients, volume expansion per se, though clearly linked with blood pressure levels, is not a factor in the genesis of diurnal BP rhythmicity [11].

Stefanski et al. found that in IgA nephropathy patients with normal insulin clearance, there was elevation of BP by day and especially by night compared with age-, gender- and body mass index (BMI)-matched control subjects [12]. Farmer et al. found that 55% of patients with diverse renal conditions but a plasma creatinine of <110 μmol/l had reduced BP fall with sleep, compared with 33% of a BP-, age-, plasma creatinine and gender-matched group of essential hypertensives [13]. Farmer et al. also showed that the proportion of patients with an attenuated fall in nocturnal BP rose progressively comparing cohorts of patients with worse renal function; very few dialysis patients retained normal diurnal BP rhythm, even those with normal daytime BP [13].

Negative end-organ consequences of abnormal diurnal BP variability have been reported in renal cohorts. A faster decline of renal function in predialysis patients has been shown by Timio et al. in hypertensive renal disease [7], by Farmer et al. in diabetic nephropathy [14] and by Csiky et al. in IgA nephropathy [15].

Increased left ventricular mass in association with nocturnal hypertension has been reported in predialysis patients [16], dialysis patients [17] and renal transplant recipients [18]. Furthermore, Covic et al. [19] demonstrated a major role for elevated nocturnal BP levels in the pathogenesis of cardiac enlargement and progressive dilatation—conditions recognized to be associated with the worst outcome/patient survival. A persistent loss of diurnal BP rhythm was identified as an independent risk factor for the development of dilated cardiomyopathy in stable, normotensive
It is the purpose of this review to critically examine only the solid evidence supporting the use of ABPM, as a better prospective assessment strategy, to determine BP levels and variability.

Recent prospective trials examining the predictive power of ABPM

ABP levels

The seminal study that evaluated the prognostic value of measuring ABP was conducted in San Francisco and published in 1983 by Perloff et al. [21]. Daytime BP values alone were recorded—a consequence of the use of monitors—and the investigators compared office and ABP by calculating the difference between these measures and applying simple regression analysis. Event rates and life-table analyses over a 10-year period demonstrated a greater cumulative incidence of fatal and non-fatal cardiovascular events in those subjects with higher ABP (but not office BP) levels.

From 1987 there was a prospective 10-year population-based study of ABP in Ohasama, Japan. Using a large cohort of 1572 subjects, the prognostic value of ABP was assessed using a Cox proportional hazards model. The subjects were divided into quintiles of screening BP and ABP. There was no relationship between cardiovascular outcomes and screening BP values. However, a ‘U’-shaped relationship with cardiovascular and indeed total mortalities was reported when ABP values were used; this was highly reminiscent of the cross-sectional association between mortality and BP in dialysis cohorts. The authors speculated that confounders such as cancer and severe heart disease might have caused this association, although lack of proper statistical adjustment for diabetes and cholesterol values were clearly significant methodological limitations [22].

Solid confirmation of the strong relevance of ABP levels was provided by invasive ambulatory measurement of BP. Four hundred and seventy-nine hypertensive patients underwent a 24-h intra-arterial BP monitoring session between 1979 and 1993 [23,24]. The subjects were classified into 126 individuals with ‘office’ and 353 with sustained (defined as above) hypertension. Over an average of 9 years, patients were studied for the prevalence of target-organ damage and cardiovascular events. Patients with office hypertension had an 11% incidence of left ventricular hypertrophy compared with 38% for the sustained hypertension cohort \((P<0.0001)\). Of the office hypertension group, 11.6% had experienced an adverse cardiovascular event compared with 22.7% of the sustained hypertension group \((P<0.001)\).

In a yet larger series using the same approach [25], the study population consisted of 688 patients with a mean \((\pm SD)\) age of 51 ± 11 years who had undergone pre-treatment, 24-h, intra-arterial ABPM on the basis of elevated clinical blood pressure. A total of 157 first events were recorded during a 9.2 ± 4.1-year follow-up period demonstrated a greater cumulative incidence of fatal and non-fatal cardiovascular events in those subjects with higher ABP (but not office BP) levels.
period. The predictive value of a regression model including age, sex, race, BMI, smoking, diabetes mellitus, fasting cholesterol level and previous history of cardiovascular disease was significantly improved by the addition of any ambulatory systolic or diastolic blood pressure parameter (whether 24-h, daytime or night-time mean) or pulse pressure, whereas the inclusion of baseline clinical blood pressure variables did not enhance the prediction of events. The most predictive models contained the ambulatory systolic blood pressure parameters. In the model containing 24-h mean ambulatory systolic blood pressure, age \( (P < 0.001) \), male sex \( (P < 0.001) \), South-Asian origin \( (P = 0.008) \), diabetes mellitus \( (P = 0.05) \) and previous cardiovascular disease \( (P < 0.001) \) were additional independent predictors of events. Whereas 24-h ambulatory systolic blood pressure was related in a linear fashion to the incidence of both coronary and cerebrovascular events, 24-h ambulatory diastolic blood pressure exhibited a similar positive linear relationship with cerebrovascular events, but a curvilinear relationship with coronary events. The investigators concluded that ABP was superior to clinical measurement for the assessment of cardiovascular risk and that there was no reduction in coronary risk at lower levels of ambulatory diastolic blood pressure. The problem with these studies is that intra-arterial BP is not the same thing as non-invasive BP derived from oscillatory analysis using an upper-arm compression cuff, but the difference in outcome for ‘white-coat’ compared with sustained hypertension patients is telling.

**ABP circadian variability**

More than a decade after the initial reports suggesting the greater relevance of BP levels measured by ABPM, the first longitudinal studies emerged to support an important role for abnormal diurnal variability. Zweiker et al. performed a study involving 116 treated hypertensive patients followed for an average of 31 months [26]. The investigators found a significantly higher rate of cardiovascular complications in ‘non-dippers’ (four events, 29 subjects) compared with ‘dippers’ (one event in 87 subjects). At the same time, the preliminary data from the Progetto Ipertensione Umbria Monirraggio Ambulatoriale (PIUMA) were reported [27]. All 1187 patients in the initial study underwent 24-h ABPM, echocardiography and metabolic and clinical assessments. Using BP data from similar large Italian normotensive cohorts, the investigators were able to classify subjects into those that were normotensive, office-hypertensive and ABP-hypertensive (24-h or day-to-night diurnal BP difference). In a follow-up period of 3.5 years, the office-hypertension group had a cardiovascular event rate similar to the normotensive group, while the event rate in the ‘non-dipping’ subgroup of the sustained hypertensive subjects was three times that of the ‘dipping’ subgroup. Further follow-up studies also tried to characterize the impact of short-term BP variability (using the standard deviation of BP levels as a surrogate), but these results were confounded by age and a higher prevalence of diabetes (see [27]).

More recently, Jan Staessen’s group has examined the incremental value of ambulatory BP over and above office BP. He undertook a substudy based upon the Syst-Eur trial (starting in October 1988, finishing in February 1999). A total of 808 older (>60 years) patients whose untreated systolic BP (SBP; conventionally measured) was 160–219 mmHg and whose diastolic BP (DBP) was <95 mmHg were randomized to nitrendipine and/or hydrochlorothiazide, or placebos [28]. The outcome measures were total and cardiovascular mortality, and all cardiovascular end-points (fatal and non-fatal stroke and cardiac). After adjusting for gender, age, previous cardiovascular events, smoking and geography, a 10-mmHg higher conventional SBP at randomization was not associated with a worse prognosis, whereas a 10 mmHg elevation in 24-h ABP was associated with a 1.2- to 1.4-fold increased hazard ratio for most outcomes. More importantly, patients who lacked a nocturnal decline in SBP had a greater incidence of stroke and myocardial infarction than patients with normal diurnal BP variation.

Further evidence supporting a strong relationship between stroke and abnormal circadian variability was provided by Yamamoto et al. [29], who followed 105 patients with symptomatic lacunar infarcts by monitoring 24-h ABP. Follow-up over 3 years showed that in the group with subsequent further neurological events and silent lacunae, the day-to-night ABP reduction was much less (1.3% SBP, 3.3% DBP) than in the group with no sequelae (7.2% SBP, 10.4% DBP). Very recently, Kario et al. [30] reported on the relationship between the extremes of dipping and non-dipping and stroke, by studying stroke events in 575 older Japanese patients with sustained hypertension determined by ABPM (without medication). They were subclassified by their nocturnal fall in SBP (97 extreme dippers, with >20% nocturnal fall in SBP; 230 dippers, with 10–20% fall; 185 non-dippers, with 0–10% fall; and 63 reverse dippers, with >0% fall) and were followed prospectively for an average duration of 41 months. Baseline brain magnetic resonance imaging (MRI) disclosed that the percentages with multiple silent cerebral infarct were 53% in extreme dippers, 29% in dippers, 41% in non-dippers and 49% in reverse dippers. There was a J-shaped relationship curve between dipping status and stroke incidence (extreme dippers, 12%; dippers, 6.1%; non-dippers, 7.6%; and reverse dippers, 22%), and this remained significant in a Cox regression analysis after controlling for age, gender, BMI, 24-h SBP and antihypertensive medication. Intracranial haemorrhage was more common in reverse dippers (29% of strokes) than in other subgroups (7.7% of strokes, \( P = 0.04 \)). In the extreme dipper group, 27% of strokes were ischaemic strokes that occurred during sleep (compared with 8.6% of strokes in the other three subgroups, \( P = 0.11 \)).
In conclusion, in older Japanese hypertensive patients, extreme dipping of nocturnal blood pressure may be related to silent and clinical cerebral ischaemia through hypoperfusion during sleep or an exaggerated morning rise in BP, whereas reverse dipping may pose a risk for intracranial haemorrhage. Excessive dipping has also been associated with ocular crises due to retinal hypoperfusion [31].

A study that may have special relevance to dialysis patients was carried out by Nakano et al. [32], who assessed the significance of reversed (i.e. nocturnal BP higher than diurnal BP) circadian BP rhythms as a predictive factor of vascular events in non-insulin-dependent diabetes mellitus (NIDDM). Vital status after an average 4-year follow-up was determined in NIDDM subjects, in whom the circadian BP profile was analysed. Two hundred and one subjects had a normal circadian BP rhythm (group N) and the remaining 87 had a reversed one (group R). There was no difference in sex, glaucosylated haemoglobin (HbA1c), the prevalence of smokers, serum lipids or serum electrolytes between groups N and R at baseline, whereas age, the prevalence of hypertension, serum creatinine and diabetic complications were more pronounced in group R than in group N. During the follow-up period (which averaged 52 months in group N and 36 months in group R), fatal and non-fatal vascular (cerebrovascular, cardiovascular, peripheral vascular arteries and retinal artery) events occurred in 20 subjects in group N and 56 in group R. The Cox proportional hazards model, adjusted for age, sex, circadian BP pattern, duration of diabetes, therapy for diabetes, various diabetic complications and hypertension, demonstrated that only circadian BP pattern and age exhibited significant relative risks for fatal events, while diabetic nephropathy, postural hypotension and hypertension, as well as circadian BP pattern exhibited significant relative risks for various non-fatal vascular events. These results suggest that reversed circadian BP rhythm was associated with occurrences of both fatal and non-fatal vascular events in NIDDM subjects. Reversed diurnal BP rhythm is common in patients on dialysis and shortly after renal transplantation (in up to 33% of cases according to our own observations).

Finally, in the one prospective study using ABPM in dialysis patients, 57 treated hypertensive haemodialysis patients (56.87 ± 16.22 years of age; 30 males, 27 females) underwent ABPM in the period between two dialysis sessions. The outcome event studied was cardiovascular death; kidney transplantation and deaths not related to cardiovascular disease were censored. The duration of follow-up was 34.4 ± 20.39 months, during which 10 cardiovascular and eight non-cardiovascular fatal events occurred. In the 10 patients who died from cardiovascular complications, age, previous cardiovascular events, ambulatory SBP, ambulatory pulse pressure (PP) and life-long smoking levels were significantly higher, and the office diastolic BP was lower at the time of inclusion than in those who did not die from cardiovascular complications ($n = 47$). Based on a Cox analysis and after adjustment for age, sex and previous cardiovascular events, a low office DBP (relative risk (RR) 0.49; 95% CI 0.25–0.93; $P = 0.03$), an elevated 24-h PP (RR 1.85; 95% CI 1.28–2.65; $P = 0.009$) and an elevated nocturnal SBP (RR 1.41; 95% CI 1.08–1.84; $P = 0.01$) were found to be predictors of cardiovascular mortality (RR associated with a 10 mmHg increase in BP and PP). This study demonstrated that nocturnal BP and 24-h PP are independent predictors of cardiovascular mortality in treated hypertensive haemodialysis patients [33].

Conclusions

There is now little doubt that ABPM is a superior method for predicting adverse cardiovascular outcome in untreated and treated hypertensive patients, and also in normotensive subjects. This is not only because it is a more accurate method, revealing unsustained hypertensives, but it is also the only method capable of assessing the important issue of diurnal BP variation, which has its own prognostic relevance. Although the reproducibility of diurnal BP rhythm is limited in hypertensive and also renal patients [19,34], it is probably a marker for poor autonomic function and possibly adverse structural arterial changes [35], which have their own prognostic importance [36] for dialysis patients. Thus, diurnal BP rhythm may be a ‘blunt axe’, but even a blunt axe may fell a tree. It is also important to understand that at least in essential hypertension, diurnal BP rhythm can be successfully modulated using targeted $\alpha$-blockade with doxazosin [37]. Similar studies should therefore be undertaken in renal patients.

Given the marked short-term variability in BP shown by patients with renal disease, and their blunted, often reversed, diurnal BP variability, there is a clear rationale for the routine use of ABPM for renal patients, both in research and in daily clinical management.

References

Ambulatory blood pressure monitoring


