Predictors of All-Cause Mortality in Clinical Ambulatory Monitoring
Unique Aspects of Blood Pressure During Sleep

Iddo Z. Ben-Dov, Jeremy D. Kark, Drori Ben-Ishay, Judith Mekler, Liora Ben-Arie, Michael Bursztyn

Abstract—The prognostic value of sleep blood pressure reported by recent studies is variable. Our aim was to examine the relationship of sleep blood pressure, measured by 24-hour ambulatory blood pressure monitoring, with all-cause mortality. We studied a cohort of 3957 patients aged 55±16 (58% treated) referred for ambulatory monitoring (1991–2005). Sleep, including daytime sleep, was recorded by diary. Linkage with the national population register identified 303 deaths during 27 750 person-years of follow-up. Hazard ratios (HRs) for mortality in Cox proportional hazards models that included age, sex, hypertension, and diabetes treatment were 1.32 (95% CI: 0.99 to 1.76) for awake hypertension (≥135/85 mm Hg), and 1.67 (95% CI: 1.25 to 2.23) for sleep hypertension (≥120/70 mm Hg). By quintile analysis, the upper fifths of systolic and diastolic dipping during sleep were associated with adjusted HRs of 0.58 (95% CI: 0.41 to 0.82) and 0.68 (95% CI: 0.48 to 0.96), respectively. In a model controlling for awake systolic blood pressure, hazards associated with reduced systolic dipping increased from dippers (>10%; HR: 1.0), through nondippers (0% to 9.9%; HR: 1.30; 95% CI: 1.00 to 1.69) to risers (<0%; HR: 1.96; 95% CI: 1.43 to 2.96). Thus, in practice, ambulatory blood pressure predicts mortality significantly better than clinic blood pressure. The availability of blood pressure measures during sleep and, in particular, the pattern of dipping add clinically predictive information and provide further justification for the use of ambulatory monitoring in patient management. (Hypertension. 2007;49:1235-1241.)

Key Words: ambulatory blood pressure monitoring ■ dipping ■ mortality ■ cohort ■ sleep blood pressure

Data generated by 24-hour ambulatory blood pressure monitoring (ABPM) have been used to predict cardiovascular morbidity, as well as cardiovascular and all-cause mortality.1-9 There is mounting evidence that this predictive ability is in part unrelated to clinic blood pressure (BP) measurements. Conceivably, ABPM reflects physiological states that are not captured by resting clinic measurements.9 Moreover, ABPM reduces the influence of the measurement itself on BP values, namely the white-coat effect. In addition, ambulatory monitoring may unmask abnormal BP values that were not detected in the office. Thus, it is expected that ABPM would predict mortality above and beyond clinic measurements. There is still debate, however, whether in reality this is indeed the case and whether the use of this burdensome technique in clinical care is justified and contributes to patient management.8

Another issue under debate concerns which component of the 24-hour ambulatory monitoring incorporates the most valuable prognostic information. Measurements taken during the waking state reflect, in part, physical activity, which may differ within and between patients. Thus, we hypothesized that, compared with awake BP, sleep measurements would relate to prognosis in a more profound way. Indeed, some1,3,5,7,10,11 but not all9 of the outcome studies have suggested this previously.

In this study, we investigated all-cause mortality among patients who underwent ambulatory monitoring in a single center since 1991. We highlight sleep BP data identified by recorded sleeping periods, including afternoon naps.12 We show that sleep BP, as well as nocturnal BP reduction (dipping, a somewhat controversial and infrequently studied topic7,9,10,13) have independent predictive power.

Methods

Study Population

Data were extracted from our entire ABPM service database, from 1991 through 2005. All of the patients were included, except those <16 years old, pregnant women, and subjects with poor-quality ABPM (<50 valid measurements). Patients were referred for standard clinical indications at the discretion of the referring physician (mainly primary care practitioners, who have been shown to use ABPM for appropriate indications8). We were not involved in the clinical care of these patients. Baseline data collected included demographic characteristics (age: 55 years [range: 16 to 93 years], sex (53% female), ethnicity (94% Jewish and 6% non-Jewish, predominantly Moslem Arabs), height (1.67 m; range: 1.27 to

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ABPM and Definitions

Twenty-four–hour ABPM was executed with Spacelabs 90207, as described previously.15 Before 1999, we used Accutracker II (Sun-tech).16,17 The monitor was mounted on the nondominant arm between 8:00 AM and 10:00 AM and removed 24 hours later. Recordings were made every 20 minutes between 6:00 AM and midnight and every 30 minutes between midnight and 6:00 AM. A mercury sphygmomanometer was initially attached to the monitor by a trained technician after the subject had been in a sitting position for at least 5 minutes (within a range of 5 mm Hg). Cuff size was selected according to measured arm circumference:

- 24-cm pediatric cuff
- 24- to 32-cm standard adult cuff, and greater than 32-cm large adult cuff. The average of 2 to 3 initial sphygmomonanometer measurements, taken by a trained technician, after the subject had been in a sitting position for 5 minutes, was considered the patient’s manual BP (normal: <140 mm Hg systolic and <90 mm Hg diastolic).18,19 Sleep, including daytime naps (reported in 31%), was logged in a diary. The terms “awake” and “sleep” BP refer to the averages of all of the measurements taken during periods of wakefulness and sleep, respectively, according to the log. Patients were classified as having normal awake BP if the corresponding value was <135 mm Hg systolic BP (SBP) and <85 mm Hg diastolic BP (DBP). Normal sleep BP was considered <120/70 mm Hg.20,21 The overall 24-hour normality definition was <125/80 mm Hg.13 The normal dip was defined separately for SBP and DBP as ≥10% reduction in BP during sleep compared with the awake period.22,23 Nondipping was defined as a decrease <10% but ≥0%. Dipping beyond 20% was considered “extreme,” and sleep-related BP “rising” denoted negative dipping.

Statistical Analyses

Baseline characteristics were compared according to outcome using χ² or t tests, as appropriate. Hazard ratios (HR) for death by these characteristics were computed by Cox regression. Variables that were found significant in univariate models were included in the multivariate analyses. Age and sex were forced into multivariate models, because these are fundamental biological characteristics. BMI was dropped in the revised version because it did not meet these criteria and had a trivial effect on the coefficients when included. Adjusted HR for mortality was also computed for BP thresholds and levels, for ambulatory BP measures expressed as continuous terms, and for quintiles of ambulatory BP measures, including dipping category (the comparison of quintiles was done by recoding the quintiles with their median BP values and testing both for trend [degrees of freedom=1], and for quintile-specific hazards [degrees of freedom=4]). Manual BP was also entered into the ambulatory models. Finally, the independent contributions of ambulatory awake versus sleep BP were assessed by Cox models, which included the baseline covariates and the 2 BP variables being compared.1 Tests for interaction of antihypertensive treatment with the main BP variable of interest in each Cox model were not significant (P>0.3). The assumption of proportional hazards, as assessed by introducing each predictor also as a time-dependent covariate, held in all of the Cox models. Independent demographic predictors for nondipping patterns were identified by multivariate logistic regression. To facilitate comparison with previous studies, most of the analyses are presented also for the subpopulation of patients treated for hypertension. Data are expressed as mean±SD or HR (95% CI), unless otherwise specified. Two-sided nominal P<0.05 was considered significant. Analyses were undertaken using SPSS 13.0 (SPSS Inc).

Results

Patient Characteristics and Demographic Data

During a 15-year period, 4006 patients aged 16 to 93 years underwent ambulatory monitoring in our service. The vital status of 49 patients (1.2%) could not be ascertained because of errors in identification numbers, inability to follow-up tourists and temporary residents, and so forth, leaving 3957 patients for analysis. Median duration of follow-up was 6.5 years (interquartile range: 4.0 to 10.0 years). Fatal events occurred in 303 patients during 27,750 person-years of follow-up (incidence: 10.9 deaths per 1000 person-years).

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics According to Vital Status, With Adjusted HRs for All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Characteristic</strong></td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Female, N (%)</td>
</tr>
<tr>
<td>Medicated HTN, N (%)</td>
</tr>
<tr>
<td>Medicated DM, N (%)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>Manual non-Jewish, N (%)</td>
</tr>
<tr>
<td>Manual HTN, N (%)</td>
</tr>
<tr>
<td>Awake HTN, N (%)</td>
</tr>
<tr>
<td>Sleep HTN, N (%)</td>
</tr>
<tr>
<td>SBP nondipping, N (%)</td>
</tr>
<tr>
<td>DBP nondipping, N (%)</td>
</tr>
</tbody>
</table>

HRs determined by Cox models are calculated per 1 year of age, females versus males, treated hypertension, treated diabetes, 1 BMI unit, and non-Jewish versus Jewish and abnormal versus normal BP (or BP dipping). Normality was classified as awake BP<135/85 mm Hg, sleep BP<120/70 mm Hg, and SBP or DBP dipping ≥10%. HTN indicates hypertension; DM, diabetes mellitus.

*Adjusted for age and sex.
†Adjusted forage, sex, treated hypertension, and treated diabetes.
‡Refers to patients treated for hypertension at the time of the index ambulatory monitoring.
There were no significant sex ($P = 0.5$) or BMI ($P = 0.7$) differences between patients who died during follow-up and those who did not (Table 1). As expected, patients who died before the censored date were older (68 ± 12 versus 54 ± 16 years) and had a higher prevalence of antihypertensive treatment (83% versus 56%) and of treated diabetes (19% versus 8%) than those alive at the end of follow-up (Table 1).

Data in the following sections (and the respective tables) are presented for all of the patients and for the subgroup of those treated for hypertension at the time of ambulatory monitoring. The untreated subgroup is not presented separately because of the small number of events and the consequent instability of the estimates.

**Ambulatory BP: Awake Versus Asleep**

Awake and sleep hypertension were more prevalent among patients who died before the censored date and were associated with increased adjusted mortality hazards, 1.32 (95% CI: 0.99 to 1.76) and 1.67 (95% CI: 1.25 to 2.23), respectively (Table 1). HRs according to various BP cutoffs are plotted in Figure 1. Awake SBP and sleep SBP and DBP levels, introduced both as continuous variables or in quintiles, predicted death in adjusted models (Table 2 and Figure 2). The independent predictive ability of sleep BP appeared to be superior to that of the corresponding awake BP in all of the patients, as well as in the treated subgroup. Cox proportional hazards models, which included both awake and asleep BP, in addition to baseline and treatment covariates, yielded somewhat higher HRs for sleep BP (Table 3). Prediction by pulse pressure (manual, awake, and sleep) generally resembled that of SBP (Tables 2 and 3).

**Dipping Pattern During Sleep**

An absent normal dipping BP pattern was independently predicted by increasing age ($P = 0.0001$) and BMI ($P = 0.001$),
female sex ($P=0.001$), treated hypertension, and treated diabetes (both $P<0.0001$). The absence of normal dipping was more prevalent among patients who died before the censored date (Table 1). The dipping magnitude, both systolic and diastolic, inversely predicted mortality in the adjusted models (Table 2) both in all of the patients and when restricted to treated patients. Analysis by quintiles revealed significantly reduced mortality in patients between the third and fifth quintile of dipping magnitude (Figure 2). In a separate categorical analysis, applying the commonly used dipping cutoff values of 10%, mortality increased in a stepwise mode in SBP nondippers (adjusted HR: 1.30; 95% CI: 1.00 to 1.69) and risers (adjusted HR: 1.96; 95% CI: 1.43 to 2.96) compared with dippers (overall $P<0.0001$). Extreme dippers had hazards similar to dippers (Figure 3).

Compared with subjects with normal awake BP and dipping patterns, dipping subjects with abnormal awake BPs had HRs of 1.70 (95% CI: 1.12 to 2.58, unadjusted) and 1.35 (95% CI: 0.88 to 2.05, adjusted for age, sex, treated hypertension, and diabetes mellitus). Nondipping patients with normal awake BPs had mortality HRs of 1.97 (95% CI: 1.18 to 3.30, unadjusted) and 1.55 (95% CI: 0.93 to 2.61, adjusted), whereas awake hypertensive nondipping subjects had

**Figure 2.** Ambulatory blood pressure quintiles predict mortality regardless of manual blood pressure. The total population was divided into quintiles of systolic (a) and diastolic (b) manual, awake, or sleep BP, as well as sleep-related BP dip. Mortality hazards (and 95% CIs) were plotted against the mean relevant BP (or dip) of each quintile. Model covariates included age, sex, antihypertensive treatment, and antidiabetic treatment (yes/no) and the designated BP measure. $P$ values for trends (degrees of freedom=1) and quintile-specific probability values (degrees of freedom=4) are shown in the plots.
HRs of 3.14 (95% CI: 2.06 to 4.77, unadjusted) and 1.93 (95% CI: 1.27 to 2.96, adjusted), highlighting the excess risk associated with nondipping (Figure 4). An assessment limited to hypertensive patients according to 24-hour BP and/or on antihypertensive treatment revealed that, in hypertension, nondipping of SBP predicts worse prognosis, notwithstanding adjustment for the individual’s 24-hour SBP (HR: 1.33; 95% CI: 1.04 to 1.71; Figure 5).

**Discussion**

Evidence linking ambulatory BP to mortality is accumulating.20 Several prospective studies have documented that the averaged level of ambulatory BP predicts risk of morbid events better than clinic BP.1,2,7,8,11,24–27 Ambulatory BP data from real-life clinical practice are sparse, however. This is one of the first reports from a large clinical ambulatory BP database in which information has been collected for 15 years. Another unique feature of our data concerns the accuracy of sleep BP (as opposed to nighttime BP) determination. In our database, BP measurements are routinely categorized according to actual sleeping hours as recorded, including afternoon naps. This may profoundly influence any analysis concerning sleep BP or circadian rhythms of BP.12,22,28–30 Hence, we anticipated differences from some previously reported mortality studies, at least with regard to the characteristics of sleep BP and the effect of nondipping.

Prognostic implications of ambulatory BP have been examined in population-based studies. Among residents}

### TABLE 3. Independent Associations of Ambulatory Awake Versus Sleep or SBP Versus DBP Measures in Cox Models

<table>
<thead>
<tr>
<th>Model No.</th>
<th>Model Variables*</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All Patients</td>
<td>Treated Patients</td>
</tr>
<tr>
<td>I</td>
<td>Awake SBP</td>
<td>1.04 (0.94 to 1.15)</td>
<td>1.06 (0.95 to 1.17)</td>
</tr>
<tr>
<td></td>
<td>Sleep SBP</td>
<td>1.15 (1.06 to 1.24)</td>
<td>1.14 (1.05 to 1.24)</td>
</tr>
<tr>
<td>II</td>
<td>Awake DBP</td>
<td>0.95 (0.87 to 1.03)</td>
<td>0.94 (0.86 to 1.03)</td>
</tr>
<tr>
<td></td>
<td>Sleep DBP</td>
<td>1.13 (1.05 to 1.21)</td>
<td>1.16 (1.07 to 1.25)</td>
</tr>
<tr>
<td>III</td>
<td>Awake SBP</td>
<td>1.24 (1.14 to 1.35)</td>
<td>1.26 (1.15 to 1.37)</td>
</tr>
<tr>
<td></td>
<td>Awake DBP</td>
<td>0.94 (0.87 to 1.01)</td>
<td>0.95 (0.87 to 1.02)</td>
</tr>
<tr>
<td>IV</td>
<td>Sleep SBP</td>
<td>1.21 (1.12 to 1.30)</td>
<td>1.19 (1.10 to 1.29)</td>
</tr>
<tr>
<td></td>
<td>Sleep DBP</td>
<td>0.96 (0.89 to 1.04)</td>
<td>0.99 (0.91 to 1.07)</td>
</tr>
<tr>
<td>V</td>
<td>Awake PP</td>
<td>1.04 (0.92 to 1.18)</td>
<td>1.06 (0.93 to 1.22)</td>
</tr>
<tr>
<td></td>
<td>Sleep PP</td>
<td>1.18 (1.06 to 1.33)</td>
<td>1.16 (1.02 to 1.32)</td>
</tr>
</tbody>
</table>

HRs were computed per 10 mm Hg for SBP or pulse pressure and 5 mm Hg for DBP. PP indicates pulse pressure.

*In addition to the specified variables, each model included age, sex, treated hypertension, and treated diabetes.

†Patients treated for hypertension at the time of the index ambulatory monitoring.

‡P<0.001; §P<0.01; ||P<0.05.

HRs of 3.14 (95% CI: 2.06 to 4.77, unadjusted) and 1.93 (95% CI: 1.27 to 2.96, adjusted), highlighting the excess risk associated with nondipping (Figure 4). An assessment limited to hypertensive patients according to 24-hour BP and/or on antihypertensive treatment revealed that, in hypertension, nondipping of SBP predicts worse prognosis, notwithstanding adjustment for the individual’s 24-hour SBP (HR: 1.33; 95% CI: 1.04 to 1.71; Figure 5).

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Prognostic implications of ambulatory BP have been examined in population-based studies. Among residents...
of Ohasama, Japan, and Copenhagen county, Denmark, ambulatory BP had a stronger predictive power than clinic BP. In contrast to our study of referred patients, in the Danish population, the dipping pattern had prognostic implications only for subjects with daytime hypertension. However, in Ohasama residents, the nocturnal BP decline predicted cardiovascular mortality independent of the 24-hour average, that is, nondipping was a risk factor for mortality regardless of 24-hour BP normality (defined as <135/80 mm Hg). These results are consistent with our study, despite our more strict ambulatory BP cutoff points (many normotensive by Ohasama threshold would have been deemed hypertensive by current definitions). Mortality risk was better determined by nighttime than daytime measurements in Monza, Italy (the population-based Pressioni Arteriose Monitorate e Loro Associazioni Study), but the overall predictive value of ambulatory (or home) BP did not exceed that of clinic BP, and dipping was not examined. Interpretation of the Pressioni Arteriose Monitorate e Loro Associazioni results is complicated by the fact that the models used did not include covariates strongly related to mortality, such as age and sex.

Mortality analyses of our database generally validate previous reports of the relationship between ambulatory BP and mortality. However, we have found differences, including stronger associations than previous studies, particularly for sleep BP. In the important Office Versus Ambulatory Blood Pressure Study among treated hypertensive subjects reported by Clement et al., in which ambulatory BP did not predict all-cause mortality, ambulatory BP was associated with cardiovascular events (fatal or nonfatal), even after adjustment for office BP. Office-adjusted nighttime BP, however, did not predict fatal or nonfatal myocardial infarction or stroke. This inferiority of nighttime BP may be explained in part by the arbitrary designation of nighttime, namely from midnight to 6:00 AM. If Office Versus Ambulatory Blood Pressure participants’ sleep deviated considerably from this definition, and particularly if they had napped during daytime, then the nighttime BP reported may not reflect genuine sleep-related BP. This could also explain our ability to better associate nondipping with mortality in normotensive patients.

Patients in our study were referred by primary care physicians or subspecialists, similar to the Dublin Outcome Study, which also examined a referred population. In Dublin, however, patients were off of treatment at the time of baseline ambulatory monitoring. For nighttime BP, measurements taken between 1:00 AM and 6:00 AM were averaged. Higher ambulatory BP (24-hour, daytime, or nighttime) was associated with significantly increased cardiovascular mortality. Nighttime SBP provided additional predictive information over daytime values (which had inverse HRs). Thus, our findings, predominantly in treated subjects, are generally in line with those of the single-center off-treatment study from Ireland, although we observed larger HRs than those reported by Dolan et al. In addition, unlike our analyses, dipping was not specifically evaluated in the Dublin Outcome Study. Analysis of mortality data according to sleep-related BP dipping status or magnitude is justified in light of the mass of evidence connecting the nondipping pattern with clinically apparent target organ damage (eg, stroke, left ventricular hypertrophy, microalbuminuria, renal dysfunction, intimal–medial thickness, and morbidity and mortality).

Some limitations of our study should be discussed. First, in our study design we could not account for treatment changes in response to the ambulatory monitoring and subsequent BP changes. Furthermore, the need to assess follow-up BP in outcome studies has been pointed out. Second, we do not have information on smoking, hyperlipidemia, and previous cardiovascular diseases. Third, we studied referred treated and untreated patients who may not necessarily be representative of hypertensive populations. Referral bias may have influenced the generalizability of our results. Forth, we report outcome only for all-cause mortality. In previous studies, clinic and ambulatory BPs generally had a stronger association with cardiovascular rather than total mortality. Therefore, our results may actually underestimate the true prognostic value of ambulatory BP.

**Perspectives**

ABPM data, collected in the outpatient setting in a manner that differentiates between genuine wakefulness and sleeping periods, reveal durable all-cause mortality associations with sleep BP and dipping magnitude. These associations are stronger than corresponding relations with manual or awake BP. These findings are in line with the view held by one of the forefathers of the field of hypertension research, Sir Frederick Horace Smirk, who believed that there are 2 components of BP. He defined the basal component essentially as the lowest achieved at the maximum relaxation state before rising and the supplemental one as the difference between the casual and basal values. These components roughly correspond with sleep BP and dipping magnitude in 24-hour ABPM. He found the basal measure to have a stronger implication for life expectancy than the casual one. Our findings are consistent with Smirk et al., and suggest that sleep BP data, generated by ambulatory monitoring, add substantial prognostic information in everyday clinical practice.

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**Disclosures**

None.

**References**


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