Sleep and Ambulatory Blood Pressure

Ambulatory Blood Pressure and Cardiovascular Outcome in Relation to Perceived Sleep Deprivation

Paolo Verdecchia, Fabio Angeli, Claudia Borgioni, Roberto Gattobigio, Gianpaolo Reboldi

Abstract—Sleep deprivation induced by cuff inflations during overnight blood pressure (BP) monitoring might interfere with the prognostic significance of nighttime BP. In 2934 initially untreated hypertensive subjects, we assessed the perceived quantity of sleep during overnight BP monitoring. Overall, 58.7%, 27.7%, 9.7%, and 4.0% of subjects reported a sleep duration perceived as usual (group A), <2 hours less than usual (group B), 2 to 4 hours less than usual (group C), and >4 hours less than usual (group D). Daytime BP did not differ across the groups (all Ps not significant). Nighttime BP increased from group A to D (124/75, 126/76, 128/77, and 129/79 mm Hg, respectively; all Ps for trend <0.01). Over a median follow-up period of 7 years there were 356 major cardiovascular events and 176 all-cause deaths. Incidence of total cardiovascular events and deaths was higher in the subjects with a night/day ratio in systolic BP >10% compared with those with a greater day–night BP drop in the group with perceived sleep duration as usual or <2 hours less than usual (both P<0.01), not in the group with duration of sleep ≥2 hours less than usual (all Ps not significant). In a Cox model, the independent prognostic value of nighttime BP for total cardiovascular end points and all-cause mortality disappeared in the subjects with perceived sleep deprivation ≥2 hours. In conclusion, nighttime BP rises and loses its prognostic significance in the hypertensive subjects who perceive a sleep deprivation by ≥2 hours during overnight monitoring. (Hypertension. 2007;49:777-783.)

Key Words: hypertension • dippers • nondippers • blood pressure monitoring • sleep • stroke • myocardial infarction • epidemiology

Despite the growing body of evidence supporting the prognostic value of nighttime blood pressure (BP),1–6 it is unclear to what extent the compressive, tactile, and sonorous stimuli produced by repeated cuff inflations during 24-hour ambulatory BP (ABP) monitoring interfere with nighttime BP measurements, possibly through sleep disturbance or deprivation. In a study, intra-arterial ABP did not differ during day and night in the presence versus absence of concomitant noninvasive ABP monitoring.7 Studies carried out in sleep laboratories produced conflicting results in showing no changes8 and an increase9,10 in the number of nocturnal awakenings during overnight monitoring. The picture is complicated by the finding that hypertensive subjects with a blunted day–night fall in BP (“non-dippers”)11 present more frequent microarousals12 and apneic snoring13 as compared with subjects with normal day–night BP fall, but evidence is controversial.14

Overall, available studies suggest that nighttime BP could be altered by the sleep noise induced by repeated cuff inflations but do not clarify the prevalence of this phenomenon or, more importantly, its prognostic significance. The clinical impact of this issue is relevant because of the growing reliance on nighttime BP when interpreting results of ABP monitoring. Thus, the aim of the present study was to determine the prevalence of perceived sleep deprivation and its potential influence on the prognostic value of nighttime BP in a large cohort of initially untreated subjects with essential hypertension.

Methods

The Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) Study, established in June 1986, is a prospective observational registry of morbidity and mortality in initially untreated subjects with essential hypertension. The registry has been approved by the ethical committee of our National Health System, and all of the subjects provided their informed consent to participate. Details of the study have been published.15 Entry criteria include an office BP ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic on ≥3 visits and absence of secondary causes of hypertension, previous cardiovascular disease, and life-threatening conditions. BP was measured by a physician with a mercury sphygmomanometer with subjects sitting and relaxed for ≥10 minutes. Cuff size was adjusted to arm circumference. Three measurements were averaged for analysis. Systolic and diastolic BP were identified by Korotkoff phases I and V. Twelve-lead ECG was recorded at 25 mm/s and 1 mV/cm calibration. Subjects with complete right or left bundle branch block, previous myocardial infarction, Wolff–Parkinson–White syndrome, and atrial fibrillation at entry were excluded. None of the subjects...
was being treated with digitalis. Diagnosis of left ventricular hypertrophy by ECG was made by using a score developed in our laboratory, which requires positivity of ≥1 of the following 2 criteria: sum of amplitude of S wave in lead V3 and R wave in lead aVL >2.4 mV (men) or >2.0 mV (women) or typical left ventricular strain. Diabetes was diagnosed using the American Diabetes Association criteria of a fasting plasma glucose of ≥7.0 mmol/L (126 mg/dL) or current antidiabetic therapy.

**ABP**

ABP was recorded using an oscillometric device (SpaceLabs 5200, 90202, and 90207, SpaceLabs). Frequency of measurements was set to 1 every 15 minutes throughout the 24 hours. Daytime and nighttime ABP were defined through arbitrarily defined narrow fixed-clock intervals (from 10:00 AM to 8:00 PM for daytime and from midnight to 6:00 AM for night). The use of narrow fixed-clock intervals excludes the morning and evening transitional periods, during which a variable proportion of subjects is actually awake or asleep, and may provide an accurate estimate of the actual BP values during sleep and wakefulness, at least in subjects going to bed and arising in reasonably well-defined time intervals. Nondippers were defined by a nighttime/daytime ratio of ambulatory systolic BP >10%, and dippers were defined by a ratio of 1 every 15 minutes throughout the 24 hours.

At the end of the monitoring session, subjects filled a questionnaire focused on the quality of sleep during overnight BP monitoring. The questionnaire included the hour of retiring, the hour of rising, the perceived duration of sleep, and the difference in sleep duration from usual (ie, in the absence of ABP monitoring) scored as "as usual," "<2 hours less than usual," "2 to 4 hours less than usual," and ">4 hours less than usual.

Shift workers were excluded from the study. Reproducibility of ABP readings in our subjects has been examined in a previous study in which a random sample of untreated hypertensive subjects included in the PIUMA registry repeated 24-hour BP monitoring within 3 to 5 days. The between-session coefficient of variability (SD of the mean of the paired differences between 2 sessions divided by the average of all paired means) was 5.9%/6.3% for daytime BP and 6.1%/6.3% for nighttime BP.

**Follow-Up**

Family doctors were in charge of follow-up of patients in close collaboration with our hospital staff. Treatment was tailored individually and based on lifestyle and pharmacological measures. Results of baseline 24-hour ABP monitoring were made available to family doctors, and it is difficult to establish to what extent these results influenced the management of the single subjects. Thiazide diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II antagonists, calcium-channel blockers, and α1-blockers, alone or combined, were the antihypertensive drugs most frequently used. Periodic contacts with family doctors and telephone interviews and clinical visits with patients continued in order to ascertain the vital status and the occurrence of events.

**Assessment of End Points**

Hospital records and other sources of documents of patients who died or suffered a cardiovascular event were reviewed in conference by the authors of this study. Total cardiovascular events and all-cause mortality were considered terminating end points. Cardiovascular events included new-onset coronary heart disease (fatal and nonfatal myocardial infarction or angina with concomitant ischemic ECG changes), fatal and nonfatal stroke, transient cerebral attack, symptomatic aorto-iliac occlusive disease verified at angiography, congestive heart failure requiring hospitalization, other cardiovascular deaths, and renal failure requiring dialysis. The international standard criteria used to diagnose outcome events in the PIUMA study have been described. Stroke was defined as a new neurological deficit lasting >24 hours, in the absence of underlying potentially important nonvascular causes. Transient ischemic attack was diagnosed by a neurologist or internist in the presence of a rapid onset of a focal neurological deficit lasting >30 seconds and <24 hours and presumably because of ischemia. The PIUMA protocol required the deficit to be present during the qualifying clinical examination to be accepted and coded as a terminating event.

**Data Analysis**

Data analysis was performed using SPSS 13.0 release (SPSS Inc.). Parametric data are reported as mean±SD. For subjects who experienced multiple events, analysis was restricted to the first event. Comparison between the groups was carried out through 1-way ANOVA for continuous variables and χ² test for categorical variables. Multiple Tukey’s tests were carried out on continuous variables in case of significant F value in the ANOVA. Survival curves were estimated using the Kaplan–Meier product-limit method and compared by the Mantel (log-rank) test. The effect of prognostic factors on survival was evaluated by the stepwise Cox semiparametric regression model. We tested the following variables: age, sex (women and men), diabetes (no or yes), serum cholesterol (milli-moles per liter), smoking habits (current smokers and nonsmokers), body mass index (kilograms per meter squared), left ventricular hypertrophy at ECG (no or yes), antihypertensive therapy at the follow-up contact (lifestyle measures and drug treatment), type of BP recorder (5200, 90202, and 90207), office systolic and diastolic BP, and daytime and nighttime systolic and diastolic BP. In the analysis carried out in the overall population, the interaction term between sleep deprivation category (<2 hours versus ≥2 hours less than usual) and nighttime BP was forced into the model. Two-sided P≤0.05 was considered statistically significant.

**Results**

Overall, 3254 subjects were consecutively included in the PIUMA registry from June 10, 1986, to June 10, 2004. Complete follow-up information was available for 2934 of these subjects as of June 10, 2006. Mean age was 50.9 years, and women composed 45.8% of the subjects. Mean body mass index was 26.8 kg/m² (±4 kg/m²). At entry, office BP was 157/97 mm Hg (±19/10 mm Hg). Average daytime BP was 143/93 mm Hg (±14/10 mm Hg), and nighttime BP was 125/76 mm Hg (±17/11 mm Hg). Subjects with diabetes were 8.5%, and current smokers were 23.6%. The 320 subjects (9.8%) lost to follow-up were younger (47.2 years), more frequently smokers (29.3%), and less frequently diabetics (4.7%) than those with available follow-up data (all P<0.05). Daytime and nighttime ABP did not differ (all Ps not significant) between the 2 groups.

**Correlates of Perceived Sleep Deprivation**

The distribution of perceived sleep duration in terms of difference from usual is reported in Figure 1. Overall, 1715 (58.7%), 810 (27.7%), 283 (9.7%), and 116 (4.0%) of subjects perceived a duration of sleep as usual, <2 hours less than usual, 2 to 4 hours less than usual, and >4 hours less than usual.

Information on sleep deprivation was missing in only 10 subjects. The main features of trial population in relation to the perceived sleep deprivation are reported in the Table. Daytime ABP did not differ across the 4 groups (all Ps not significant), whereas nighttime ABP progressively increased from the group with no perceived sleep deprivation up to the group with more severe sleep deprivation (124/75, 126/76, 128/77, and 129/79 mm Hg, respectively; all Ps for trend <0.01). Prevalence of nondippers in the 4 groups was 30.0%/34.9%/42.4%, and 45.7%, respectively (χ²=28.0; P<0.0001).

Nighttime ABP did not differ between the group with perceived sleep duration 2 to 4 hours less than usual and that
with more severe sleep deprivation (all Ps not significant). The latter group showed higher values of nighttime systolic and diastolic BP when compared with the 2 groups with unimpaired sleep duration (all P<0.05) or sleep duration <2 hours (all P<0.05). Figure 2 shows the 24-hour ABP profile in the 2 subsets with less severe and more severe perceived impairment of sleep.

The prevalence of subjects with perceived sleep deprivation by ≥2 hours was 12.9%, 13.5%, and 18.3% among users of SpaceLabs models 90207 (n=1849), 90202 (n=772), and 5200 (n=313), respectively (χ²=6.61; P=0.037). The night/day ratio of systolic BP was 0.87 (±0.07), 0.87 (±0.08), and 0.88 (±0.09) in the 3 groups (P<0.01 for trend).

Prognostic Implications
Over a mean follow-up time of 7.0 years (range: 1 to 19 years) there were 356 new cardiovascular events and 184 deaths from all causes. In detail, there were 16 patients with fatal stroke, 4 with fatal myocardial infarction, 14 with sudden cardiac death, 80 with nonfatal stroke, 33 with transitory ischemic attack, 71 with nonfatal myocardial infarction, 59 with new-onset coronary heart disease, 38 with heart failure requiring hospitalization, 31 with peripheral vascular disease, and 10 with renal failure requiring dialysis.

The prevalence of nondippers (night/day ratio of ambulatory systolic BP >10%) was 33.2%. The number of cardiovascular events in the subset with sleep duration as usual or <2 hours less than usual and in that with perceived sleep duration ≥2 hours less than usual was 300 and 56, respectively. The total number of deaths in the 2 groups was 157 and 27, respectively. The rate (×100 patient-years) of total cardiovascular events (±95% CIs) was 1.25 (1.06 to 1.47) and 2.77 (2.35 to 3.25) in dippers and nondippers, respectively, in the subset without perceived sleep noise or sleep duration <2 hours less than usual (log-rank test: P<0.0001). In the subset with perceived sleep duration ≥2 hours less than usual, the rate of total cardiovascular events did not differ between dippers and nondippers (rate: 1.88; 95% CI: 1.26 to 2.56 versus rate: 2.01; 95% CI: 1.25 to 2.96, respectively; log-rank test: P=0.59). A similar pattern was noted in the analysis of mortality. Total mortality rate was 0.57 (95% CI: 0.43 to 0.70) in dippers and 1.47 (95% CI: 1.19 to 1.81) in nondippers in the subset with no sleep deprivation or sleep duration <2 hours less than usual (log-rank test: P<0.0001). In the subset with perceived sleep deprivation ≥2 hours, total mortality rate was 0.70 (95% CI: 0.88 to 1.17) in dippers and 1.20 (95% CI: 0.67 to 1.83) in nondippers (log-rank test: P=0.19). Figure 3 shows the event-free survival curves for total cardiovascular events and all-cause mortality in dippers and nondippers in relation to the perceived duration of sleep during 24-hour ABP monitoring.

Features of the Population in Relation to the Perceived Duration of Sleep During ABP Monitoring

<table>
<thead>
<tr>
<th>Variable</th>
<th>As Usual</th>
<th>&lt;2 h Less Than Usual</th>
<th>2 to 4 h Less Than Usual</th>
<th>&gt;4 h Less Than Usual</th>
<th>Tukey’s Test, P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=1715)</td>
<td>(N=810)</td>
<td>(N=283)</td>
<td>(N=116)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>51.0 (12)</td>
<td>51.2 (12)</td>
<td>50.7 (13)</td>
<td>48.6 (12)</td>
<td>1.7</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.9 (4)</td>
<td>26.9 (4)</td>
<td>26.6 (4)</td>
<td>26.0 (4)</td>
<td>2.4</td>
</tr>
<tr>
<td>Known duration of hypertension, years</td>
<td>3.9 (5)</td>
<td>4.1 (6)</td>
<td>4.3 (5)</td>
<td>4.6 (6)</td>
<td>0.8</td>
</tr>
<tr>
<td>Office systolic BP, mm Hg</td>
<td>156 (18)</td>
<td>158 (19)</td>
<td>158 (19)</td>
<td>160 (22)</td>
<td>3.6*</td>
</tr>
<tr>
<td>Office diastolic BP, mm Hg</td>
<td>97 (10)</td>
<td>97 (10)</td>
<td>98 (11)</td>
<td>99 (10)</td>
<td>1.2</td>
</tr>
<tr>
<td>Office heart rate, bpm</td>
<td>75 (11)</td>
<td>75 (11)</td>
<td>76 (10)</td>
<td>78 (12)</td>
<td>3.7*</td>
</tr>
<tr>
<td>Daytime systolic BP, mm Hg</td>
<td>143 (15)</td>
<td>143 (15)</td>
<td>144 (15)</td>
<td>145 (16)</td>
<td>1.0</td>
</tr>
<tr>
<td>Daytime diastolic BP, mm Hg</td>
<td>93 (10)</td>
<td>92 (10)</td>
<td>92 (11)</td>
<td>94 (10)</td>
<td>0.9</td>
</tr>
<tr>
<td>Daytime heart rate, bpm</td>
<td>79 (10)</td>
<td>79 (9)</td>
<td>80 (9)</td>
<td>81 (10)</td>
<td>2.7*</td>
</tr>
<tr>
<td>Nighttime systolic BP, mm Hg</td>
<td>124 (16)</td>
<td>126 (17)</td>
<td>128 (17)</td>
<td>129 (19)</td>
<td>6.7*</td>
</tr>
<tr>
<td>Nighttime diastolic BP, mm Hg</td>
<td>75 (11)</td>
<td>76 (11)</td>
<td>77 (11)</td>
<td>79 (12)</td>
<td>5.2*</td>
</tr>
<tr>
<td>Nighttime heart rate, bpm</td>
<td>67 (9)</td>
<td>67 (9)</td>
<td>69 (9)</td>
<td>69 (10)</td>
<td>4.0*</td>
</tr>
<tr>
<td>Systolic BP night/day ratio</td>
<td>0.867 (0.08)</td>
<td>0.877 (0.08)</td>
<td>0.886 (0.08)</td>
<td>0.889 (0.08)</td>
<td>7.9*</td>
</tr>
<tr>
<td>Diastolic BP night/day ratio</td>
<td>0.815 (0.09)</td>
<td>0.824 (0.09)</td>
<td>0.838 (0.09)</td>
<td>0.838 (0.08)</td>
<td>8.5*</td>
</tr>
</tbody>
</table>

n.s. indicates not significant.

*P<0.05.
Separate multivariate analyses were carried out in the 2 groups with less severe and more severe perceived sleep impairment. In the group without sleep deprivation or perceived sleep duration <2 hours less than usual, for each 17 mm Hg (1 SD) increase in nighttime systolic BP, there was a 34% (95% CI: 9% to 76%) higher risk for total cardiovascular events ($P=0.003$) after adjustment for the significant influence of age, sex, diabetes, cigarette smoking, and total cholesterol/high-density lipoprotein cholesterol ratio (all $P<0.05$). Daytime systolic BP and office systolic BP lost statistical significance when nighttime systolic BP entered the model. In contrast, in the subset with more severe sleep impairment, after correction for confounders, for each 17 mm Hg (1 SD) increase in nighttime systolic BP, the

Figure 2. Twenty-four–hour blood pressure profile in relation to the perceived duration of sleep during overnight blood pressure monitoring.

Figure 3. Total cardiovascular events and all-cause mortality in dippers (night/day ratio in systolic blood pressure $\leq 10\%$) and nondippers (night/day ratio in systolic blood pressure $>10\%$) in relation to the perceived duration of sleep during overnight blood pressure monitoring. The number of subjects entering each time interval is reported in the figure.
interrupt sleep in the remaining 33%. Although heart rate inflations caused an arousal in 67% of recordings and did not differ with a generally modest influence on BP. In a study, cuff recording may increase the number of nocturnal awakenings was carried out by Parati et al. An important study that examined the influence of noninvasive ABP monitoring on the hemodynamic effects of sleep disturbances caused by cuff inflations during overnight BP monitoring. These findings are in close agreement with those reported by Manning et al. in a smaller study carried out in 79 untreated hypertensive subjects who underwent 24-hour ABP monitoring and filled a questionnaire about the perceived quality of sleep during overnight BP recording. In that study, nighttime BP was significantly higher in the subjects who reported a sleep deprivation ≥ 4 hours. Because no significant differences were found in the levels of nighttime BP between the 2 groups with sleep duration 2 to 4 hours or ≥ 4 hours less than usual, these groups were pooled and compared with the 2 groups with less severe sleep impairment. In such comparison, nighttime BP was significantly higher by ≈ 4/3 mm Hg (Figure 2) in the group with more severe sleep impairment as compared with the other group.

These findings are in close agreement with those reported by Manning et al. in a smaller study carried out in 79 untreated hypertensive subjects who underwent 24-hour ABP monitoring and filled a questionnaire about the perceived quality of sleep during overnight BP recording. In that study, nighttime BP was significantly higher in the subjects who reported that “recording caused significant disruption to normal sleep” as compared with those in whom recording “did not interrupt sleep,” whereas daytime ABP did not any significant difference between the 2 groups. Beyond the close agreement, our study and that by Manning et al. support the reliability of questionnaires for assessing the perceived sleep disturbances during noninvasive ABP monitoring.

The large patient population and the long follow-up time gave us the opportunity to define the distribution of the different levels of perceived sleep deprivation and, more importantly, to establish its prognostic impact. Neither total cardiovascular end points nor all-cause mortality differed significantly between dippers and nondippers in the 13.7% of hypertensive subjects who reported a sleep deprivation during overnight monitoring ≥ 2 hours. In these subjects, nighttime ABP lost its prognostic significance in a multivariate analysis. A potential objection might be the smaller size of the
group with more severe sleep deprivation in comparison to the other groups.

Limitations of the Study
Sleep deprivation was assessed through a questionnaire, not through electroencephalogram or other polysomnographic parameters. It would have been unrealistic to examine all of our subjects in the sleep laboratory. Furthermore, because our population was 100% white, caution is required in applying results to different ethnic groups. This point is relevant because blacks are characterized by a higher nighttime BP and a blunted day–night BP fall when compared with whites.28 A blunted day–night BP fall has also been reported in Chinese subjects.29 Although sodium sensitivity is a major determinant of a blunted day–night BP fall in blacks,30 as well as in other ethnic groups,31 it would be important to investigate the potential additional role exerted by sleep disturbances in these subjects. The relatively high frequency of measurements during night, one every 15 minutes, might have contributed to worsen the quality of sleep. It could be speculated that less frequent measurements would have induced less sleep deprivation, although with a lesser reliability of BP profile.32 The older BP recorder (5200 model) was associated with slightly more sleep deprivation and lesser day–night BP reduction when compared with the newer models. The bigger size and the greater noise by the pump during inflation might be 2 possible reasons. However, cardiovascular morbidity and all-cause mortality did not show any association with the BP recorder used in this study. Finally, because the group with more severe sleep deprivation was smaller than the other group, and the interaction term did not speculatively that less frequent measurements would have induced less sleep deprivation, although with a lesser reliability of BP profile.32 The older BP recorder (5200 model) was associated with slightly more sleep deprivation and lesser day–night BP reduction when compared with the newer models. The bigger size and the greater noise by the pump during inflation might be 2 possible reasons. However, cardiovascular morbidity and all-cause mortality did not show any association with the BP recorder used in this study. Finally, because the group with more severe sleep deprivation was smaller than the other group, and the interaction term did not achieve statistical significance in the multivariate analysis, the present study might be relatively underpowered to definitively prove a detrimental prognostic impact of nondipping pattern among subjects with severe sleep deprivation.

Perspectives
Nighttime BP rises and loses its prognostic significance in a considerable minority (13.7%) of untreated hypertensive subjects who report an appreciable sleep deprivation (≥2 hours) during 24-hour BP monitoring. These results suggest that hypertensive subjects undergoing overnight BP monitoring should be questioned about perceived sleep quality. Nighttime BP should be considered reliable as a prognostic marker in the subjects with perceived duration of sleep not different from usual or <2 hours less than usual during overnight monitoring. The results of this study should influence manufacturers in designing BP recording devices so as to make them less interfering with sleep. Also, the issue of monitoring sleep disturbance by motion logging might be given proper consideration.

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Disclosures
None.

References


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