Effects of Insufficient Sleep on Blood Pressure in Hypertensive Patients
A 24-h Study

Paola Lusardi, Annalisa Zoppi, Paola Preti, Rosa Maria Pesce, Elena Piazza, and Roberto Fogari

The influence of acute sleep deprivation during the first part of the night on 24-h blood pressure monitoring (ABPM) was studied in 36 never-treated mild to moderate hypertensive patients. According to a crossover design, they were randomized to have either sleep deprivation or a full night's sleep 1 week apart, during which they were monitored with ABPM. Urine samples for analysis of nocturnal urinary excretion of norepinephrine were collected. During the sleep-deprivation day, both mean 24-h blood pressure and mean 24-h heart rate were higher in comparison with those recorded during the routine workday, the difference being more pronounced during the nighttime ($P < .01$). Urinary excretion of norepinephrine showed a significant increase at night during sleep deprivation ($P < .05$). Blood pressure and heart rate significantly increased in the morning after a sleep-insufficient night ($P < .05$). These data suggest that lack of sleep in hypertensive patients may increase sympathetic nervous activity during the night and the following morning, leading to increased blood pressure and heart rate. This situation might represent an increased risk for both target organ damage and acute cardiovascular diseases. Am J Hypertens 1999;12:63–68 © 1999 American Journal of Hypertension, Ltd.

KEY WORDS: Sleep deprivation, hypertension, ambulatory blood pressure monitoring.

According to a report of the National Commission on Sleep Disorder Research, 30 million adults and teenagers in the United States are chronically sleep deprived.[1,2] A 9-year follow-up study found that individuals sleeping fewer than 6 h each night experienced poorer health and had a 70% higher mortality rate than those who slept 7 or 8 h each night. This association remains significant even after controlling for age, gender, race, physical health, smoking history, physical activity, alcohol consumption, and social support.[3]

The relationships among habitual sleep deprivation and premature follow-up mortality,[4,5] cardiovascular morbidity,[6] and functional disability have been reported by either longitudinal or cross-sectional studies.[7] Sleep problems and especially being exhausted upon waking are markers of subclinical heart disease and belong to the precursors of myocardial infarction.[8] In Japan, "karoshi" (sudden death caused by overwork) is such a serious socioeconomic problem that Tochikubo et al[9] recently investigated the effect of sleep deprivation due to overtime work on blood pressure (BP) and on components of the power spectrum of heart rate (HR) variability in normotensive subjects, and found that lack of sleep may increase sympathetic nervous system activity on the following day, leading to increased BP and HR. The same hemodynamic results have been achieved by us in a previous 24-h

ambulatory blood pressure monitoring (ABPM) study of acutely sleep-deprived normotensives.[10]

The aim of the present study was to evaluate the influence of acute sleep deprivation on blood pressure and heart rate in never-treated hypertensive patients.

MATERIALS AND METHODS

Thirty-nine subjects (20 men and 19 women) ranging in age from 34 to 68 years, newly diagnosed as mild to moderate essential hypertensives (diastolic BP $\geq$ 95 mm Hg), gave their informed consent to participate in the study, which was previously approved by the local ethics committee. Diagnosis of arterial hypertension was made after clinical blood pressure measurement with a mercury sphygmomanometer during three visits in 4 weeks. Mean systolic and diastolic blood pressure were 162.3 $\pm$10.1 mm Hg and 99.8 $\pm$ 5.4 mm Hg, respectively, after the 4-week period. Secondary hypertension and sleep apnea syndrome were excluded by careful history and through physical and laboratory examinations, including radiologic and endocrinologic studies. The patients affected by organ damage were excluded. All were nonsmokers, without any family history of diabetes mellitus, and had never been treated with any antihypertensive agent or cardiovascular drug. Shift workers and patients affected by major sleep complaints or without a regular sleep-wake schedule (at least 8 h sleep per night) documented by a 4-week diary were excluded. No transmeridian travel was allowed for 3 months before the study. All patients wore white collars at the administrative offices of the University of Pavia, Pavia, Italy.

Subjects underwent three 24-h ambulatory blood pressure monitorings, the first of which aimed to get the patients accustomed to the measurement device, and therefore was excluded from the analysis. Thereafter patients were randomized, according to a crossover design, to have either sleep deprivation during the first part of the night or a full night's sleep, 1 week apart, during which they were monitored with ABPM. Recordings were performed with SpaceLabs 90207 monitor (SpaceLabs Inc., Redmond, WA); it was fitted to the patients' nondominant arm at 2 PM and was programmed to measure blood pressure every 15 min throughout the whole 24-h period. Each time a reading was taken, patients were instructed to remain motionless. On the days of ambulatory monitorings patients followed their daily routine and were asked not to nap, drink caffeinated beverages or alcohol, or to perform any heavy activity.

During the full night's sleep, the sleep period was scheduled from 11 PM to 7 AM; during the sleep-deprivation night, patients slept from 3 AM to 7 AM, being subjected to a restriction of sleep to the second part of the night (50% of the total amount). To verify that physical activities were generally maintained at a constant level during either the control or the sleep-deprivation day, patients kept a detailed diary. During the sleep-deprivation phase the patients remained at home watching TV, reading, or talking. A relative or a friend prevented their falling asleep for the waking period. Twenty-four–hour recordings were excluded from analysis when more than 10% of all readings or more than one reading per hour were missing or contained error readings. Urine samples for analysis of nocturnal urinary excretion of norepinephrine were collected for 12 h, starting from 7 PM, in urinary sampling devices containing 6 mmol/L HCl. Urinary norepinephine levels were determined by high-performance liquid chromatography with electrochemical detection.

The statistical analysis of the data was performed using the SAS system version 6.04. Analysis of variance and paired Student's t test were used, with $P < .05$ taken as statistically significant. For all recordings, the first hour of measurements was not included in the statistical analysis to eliminate possible artifacts related to the beginning of the experiment.

RESULTS

Thirty-six subjects (20 men and 16 women) completed the study. Three subjects dropped out because they had a 10% or greater loss of the BP data for analysis and withdrew their consent to repeat the 24-h recordings. The main results of the present study are shown in Table 1; Figure 1 shows mean 24-h ambulatory blood pressure and heart rate values during sleep deprivation and the full night's sleep control conditions. On the whole, during the sleep-deprivation day both mean 24-h BP and mean 24-h HR were higher than during the routine workday (systolic BP [SBP] = +5.2 mm Hg, $P < .05$; DBP = + 4.3 mm Hg, NS; HR = 3.8 beats/min, NS); such a difference was to be referred to the nighttime and to the following morning. In fact BP and HR were higher during the sleep-deprivation period (11 PM–3 AM) (SBP = + 15 mm Hg, $P < .001$; DBP = + 16 mm Hg, $P < .001$; HR = + 8.3 beats/min, $P < .001$) and during the subsequent sleep hour (3 AM–7 AM) (SBP = + 5.1 mm Hg, $P < .01$; DBP = NS; HR = + 5.4 beats/min, $P < .05$) than during the routine nighttime.

During the morning hours after sleep deprivation (7 AM–12 PM) BP and HR were higher when compared with the values recorded after a full night's sleep (SBP = + 7.1 mm Hg, $P < .001$; DBP = + 4 mm Hg, $P < .01$; HR + 5.5 beats/min, $P < .05$).

When the ABPM of the control day was considered, all patients were "dippers," but all of them became "nondippers" after the acute sleep deprivation. In fact, nocturnal SBP fall was 14% during the full night's sleep condition, but only 7% during the sleep-

TABLE 1. STUDY RESULTS

Parameter	Control Workday	Sleep Deprivation Day	P
Mean 24h SBP (mm Hg)	145.09 ± 9.40	150.32 ± 7.83	.05
First part of the night SBP (mm Hg) (23:00–03:00)	131.52 ± 10.36	146.93 ± 9.37	.001
Second part of the night SBP (mm Hg) (03:00–07:00)	132.84 ± 7.38	137.95 ± 8.04	.01
Morning SBP (mm Hg) (07:00–12:00)	147.72 ± 6.84	154.86 ± 5.91	.001
Mean 24h DBP (mm Hg)	86.86 ± 7.25	91.12 ± 7.84	NS
First part of the night DBP (mm Hg) (23:00–03:00)	75.11 ± 5.68	91.07 ± 6.35	.001
Second part of the night DBP (mm Hg) (03:00–07:00)	78.76 ± 6.34	80.17 ± 6.42	NS
Morning DBP (mm Hg) (07:00–12:00)	92.28 ± 7.26	96.29 ± 7.25	.01
Mean 24h HR (beats/min)	69.79 ± 4.41	73.61 ± 5.23	NS
First part of the night HR (beats/min) (23:00–03:00)	63.67 ± 10.36	71.93 ± 10.03	.001
Second part of the night HR (beats/min) (03:00–07:00)	61.11 ± 6.25	66.51 ± 7.48	.05
Morning HR (beats/min) (07:00–12:00)	69.73 ± 5.26	75.19 ± 6.33	.05
Urinary excretion of norepinephrine (mmol/min) (19:00–07:00)	1.57 ± 0.26	2.12 ± 0.31	.05

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

deprived condition; nocturnal DBP falls were, respectively, 16% and 7%. Nocturnal HR decline was 16% during the control night and 8% during the sleep-insufficient night. Urinary excretion of norepinephrine corrected for creatinine showed a significant increase at night during sleep deprivation ($P < .05$).

DISCUSSION

The results of this study showed that, in never-treated hypertensive subjects, acute sleep deprivation during the first part of the night produced a blunted BP and HR nocturnal fall during the hours of sleep deprivation, a smaller decrease in SBP and HR during the sleeping hours after the sleep deprivation, and an increase in BP and HR values in the morning after a sleep-insufficient night. These findings are in agreement with previous observations in normotensive subjects,[9–11] even though the two groups are not comparable for their different ages, as the hypertensive patients we studied were older. However, we found higher BP and HR values during the sleeping period after the sleep deprivation and higher 24-h HR in comparison with the normotensive group,[9] suggesting a greater sympathetic activation in hypertensive subjects.

These results also point out that the nocturnal BP decline is mainly related to sleep itself and to the associated physical inactivity and postural changes rather than to the actual time of day, which confirms previous reports that the timing of the diurnal BP rhythm is determined mainly by extrinsic factors.[9–20] Thus, in patients who remained awake BP did not decrease during the first part of the night, although it was time to sleep. Likewise, we observed that, after the sleep deprivation occurring during a westward

transmeridian flight, the shift of the sleeping time blunted the BP and HR nocturnal falls in normotensive individuals.[19] This might be explained by the fact that an upright position enhances the activity of noradrenergic branches,[21] irrespective of the time of day.

The 24-h rhythm of HR seems to reflect modulatory influences that are different from those controlling nycterohemeral changes in BP; according to Van den Meiracker et al[22] postural changes have little effect on HR and the nocturnal HR decline appears mainly caused by the sleep condition. As a matter of fact, HR maintained itself higher for all the recovery sleep after the deprivation, in comparison with the control night.

Although we did not perform polysomnographic sleep recordings, we hypothesize that the acute sleep deprivation might have altered the nature of sleep itself, leading to a predominance of rapid eye movement (REM) sleep phases, during which HR reaches higher levels, similar to those during wakefulness, due to sympathetic activation.[23–25] Sympathetic activation is likely to contribute also to the significant increase in BP and HR observed in the morning after a night of insufficient sleep, which is supported by the increase in urinary excretion of norepinephrine observed during the sleep-deprivation night. Other authors observed that the normal diurnal variation of urinary catecholamine excretion is easily overridden by sustained sympathoadrenal activity,[26] and, in our opinion, sleep deprivation might represent a stressful condition promoting an increased synthesis of catecholamines through the activation of superior centers. Our findings corroborate the observations of Tochikubo et al, who pointed out an altered sympathovagal balance, with a significantly increased low frequency/high frequency (LF/HF) balance at the
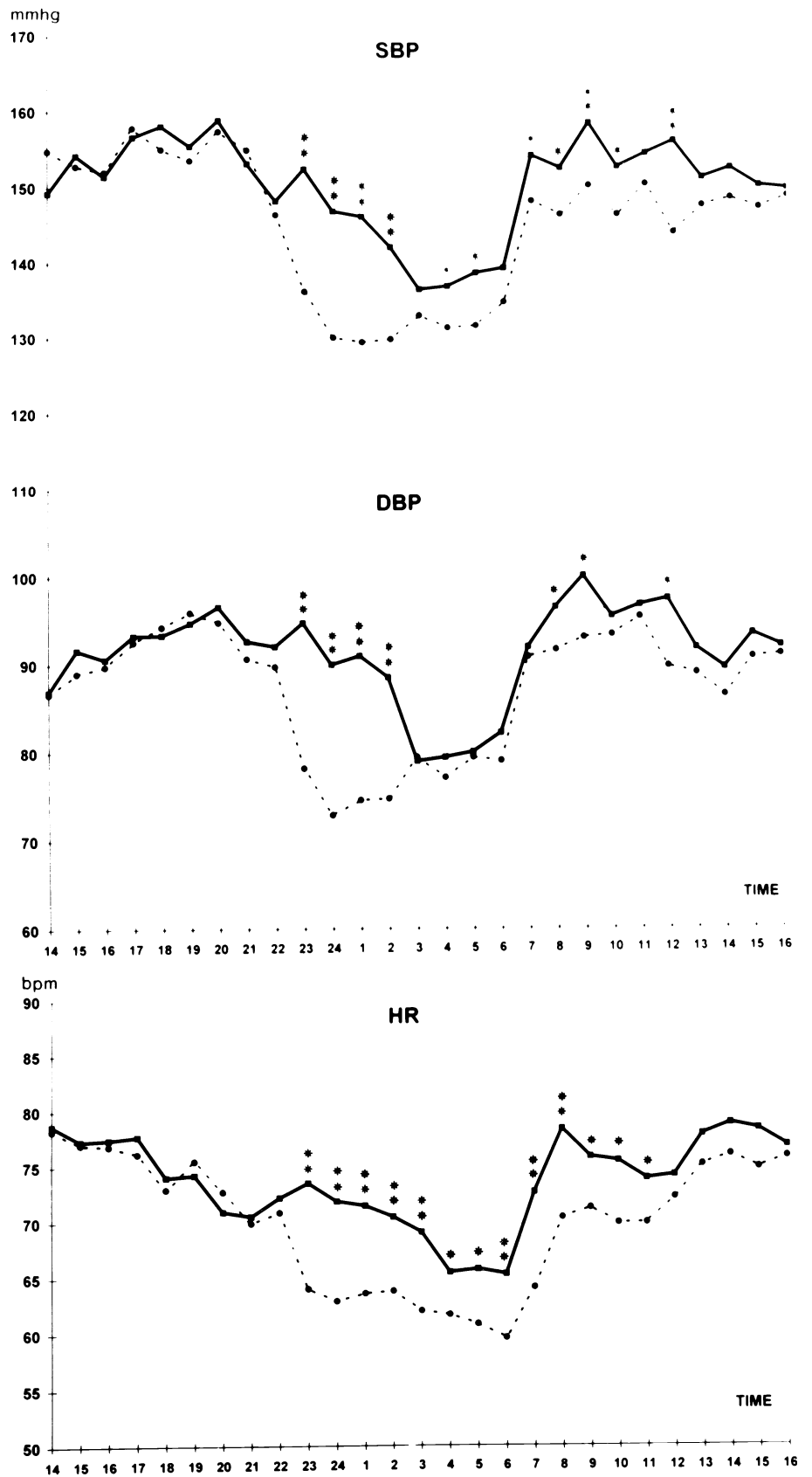
FIGURE 1. *Ambulatory blood pressure and heart rate monitorings during the sleep deprivation day (■) and the control workday (•). *P < .05; **P < .01.*

spectral analysis of RR intervals, on the day after a sleep-insufficient night.[9]

Two practical considerations descend from our observations. First, due to the blunted nocturnal BP fall, we might suppose that chronically sleep-deprived hypertensives are presumably nondippers and therefore are at higher risk of target organ damage and cardiovascular morbidity and mortality.[27–31] Secondly, the BP and HR increase observed during the morning after sleep deprivation might increase the risk of cardiovascular events, which are known to occur more frequently from early morning to noon.[32–34] Thus, in those hypertensives who habitually sleep few hours per night for various reasons, the use of long-acting antihypertensive agents able not only to ensure the nocturnal control of BP but also to blunt the early morning BP rise might be useful. Further studies, however, are needed to confirm such a hypothesis.

REFERENCES

1. Report of the National Commission on Sleep Disorders Research, U.S. Department of Health and Human Services, Vol. 2. p 84 (Washington DC,1994).

2. Bliwise DL, King AC, Harris RB: Habitual sleep duration and health in a 50-60 year old population. J Clin Epidemiol 1994;47:35–41.

3. Wingard DL, Berkman LF, Brand RJ: A multivariate analysis of health related practices: nine years mortality follow-up of the Alameda country study. Am J Epidemiol 1982;116:765–775.

4. Wingard DL, Berkman LF: Mortality risk associated with sleep patterns among adults. Sleep 1983;6:102–107.

5. Kripke DF, Simon RN, Garfinkel L, Hammond EC: Short and long sleep and sleeping pills: is increased mortality associated? Arch Gen Psychiat 1979;36:103–113.

6. Partinen M, Putkonen PTS, Kaprio J, et al: Sleep disorders in relation to coronary heart disease. Acta Med Scand 1982;660(suppl):69–83.

7. Pollak CP, Perlik D, Lisner JP, et al: Sleep problems in the community elderly as predictors of death and nursing home placement. J Commun Health 1990;15:123–135.

8. Appels AD, Schouten E: Waking up exhausted as risk indicator of myocardial infarction. Am J Cardiol 1991;68:395–398.

9. Tochikubo O, Ikeda A, Miyajima E, Ishii M: Effects of insufficient sleep on blood pressure monitored by a new multibiomedical recorder. Hypertension 1996;27:1318–1324.

10. Lusardi P, Mugellini A, Preti P, et al: Effects of a restricted sleep regimen on Ambulatory Blood Pressure Monitoring in normotensive subjects. Am J Hypertens 1996;9:503–505.

11. Mougin F, Simon-Rigaud ML, Davenne D, et al: Effects of sleep disturbances on subsequent physical performance. Eur J Appl Physiol 1991;63:77–82.

12. Clark LA, Denby L, Pregibon D, et al:A quantitative analysis of the effects of activity and time of day on the diurnal variations of blood pressure. J Chronic Dis 1987;40:671–681.

13. Pickering TG: The influence of daily activity on ambulatory blood pressure. Am Heart J 1988;116:1141–1145.

14. Baumgart P, Walger P, Fuchs G, et al: Twenty four hour blood pressure is not dependent on endogenous circadian rhythm. J Hypertens 1989;7:331–334.

15. Sudberg S, Kohvakka A, Gordin A: Rapid reversal of circadian blood pressure rhythm in shift workers. J Hypertens 1988;6:393–396.

16. Chau NP, Mallion JM, de Gaudemaris R, et al: Twenty four hour ambulatory blood pressure in shift workers. Circulation 1989;80:341–347.

17. Pickering TG, James GD: Determinants and consequences of the diurnal rhythm of blood pressure. Am J Hypertens 1993;6:166S–169S.

18. Bursztyn M, Mekler J, Wachtel N, Ben-Ishay D: Siesta and ambulatory blood pressure monitoring. Comparability of the afternoon nap and the night sleep. Am J Hypertens 1994;7:217–221.

19. Fogari R, Lusardi P, Zoppi A, et al: Effect of a westward transmeridian flight on ambulatory blood pressure monitoring in normotensive subjects. J Hypertens 1997;15:143–146.

20. Degaute JP, van de Borne P, Linkowski P, Van Cauter E: Quantitative analysis of the 24-hour blood pressure and heart rate patterns in young men. Hypertension 1991;18:199–210.

21. Dodt C, Breckling U, Derad I, et al: Plasma epinephrine and norepinephrine concentrations of healthy humans associated with nighttime sleep and morning arousal. Hypertension 1997;30[part 1]:71–76.

22. Van den Meiraker A, Man in't Veld A, van Eck HJR, et al: Determinants of short-term blood pressure variability: effects of bed rest and sensory deprivation in essential hypertension. Am J Hypertens 1988;1:22–26.

23. Mancia G: Autonomic modulation of the cardiovascular system during sleep. N Engl J Med 1993;328:347–349.

24. Somers VK, Dyken ME, Mark AL, Abboud FM: Sympathetic nerve activity during sleep in normal subjects. N Engl J Med 1993;328:303–307.

25. Jones JV, Sleight P, Smyth HS: Haemodynamics changes during sleep in man *in* Ganten D, Pfaff D (eds): Sleep: Clinical and Experimental Aspects. Springer Verlag, Berlin/Heidelberg/New York, 1982, pp 105–127.

26. Townshend M, Smith J: Factors influencing the urinary excretion of free cathecolamines in man. Clin Sci 1973;44:253–265.

27. O'Brien E, Sheridan J, O'Malley K: Dippers and nondippers (letter). Lancet 1988;ii:397.

28. Verdecchia P, Schillaci G, Gatteschi C, et al: Blunted nocturnal fall in blood pressure in hypertensive women with future cardiovascular morbid events. Circulation 1993;88:986–992.

29. Verdecchia P, Schillaci G, Guerrieri M, et al: Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. Circulation 1990;81:528–536.

30. Palatini P, Mormino P, Martina S, et al: Clinical signif-

icance of nocturnal blood pressure and blood pressure variability: analysis of 522 cases. Cardiologia 1990;35: 217–222.

31. Kobrin I, Dunn F, Oigman W, et al: Essential hypertension in the elderly: circadian variation of arterial pressure, *in* Weber MA, Drayer JIM (eds): Ambulatory Blood Pressure Monitoring. Steinkopff, Darmstadt, Germany, 1984, pp 181–185.

32. Marsh EE III , Biller J, Adams HP Jr, et al: Circadian variation in onset of acute ischemic stroke. Arch Neurol 1990;47:1178–1180.

33. Muller JE, Tofler JH, Stone PH: Circadian variation and triggers of onset of acute cardiovascular disease. Circulation 1989;79:733–743.

34. Willich SN, Levy D, Rocco MB, et al: Circadian variation in the incidence of sudden cardiac death in the Framingham Heart study population. Am J Cardiol 1987;60:801–806.