

Effects of Sleep Deprivation on Neural Circulatory Control

Masahiko Kato, Bradley G. Phillips, Gardar Sigurdsson, Krzysztof Narkiewicz,
Catherine A. Pesek, Virend K. Somers

Abstract—Effects of sleep deprivation on neural cardiovascular control may have important clinical implications. We tested the hypothesis that sleep deprivation increases heart rate, blood pressure, and sympathetic activity and potentiates their responses to stressful stimuli. We studied 8 healthy subjects (aged 40 ± 5 years, 6 men and 2 women). Blood pressure, heart rate, forearm vascular resistance, and muscle sympathetic nerve activity were measured at rest and during 4 stressors (sustained handgrip, maximal forearm ischemia, mental stress, and cold pressor test). Measurements were obtained twice, once after normal sleep and once after a night of sleep deprivation. All measurements were obtained in a blinded, randomized manner. In comparison with normal sleep, sleep deprivation resulted in an increase in blood pressure (normal sleep versus sleep deprivation = 82 ± 8 versus 86 ± 7 mm Hg, mean \pm SEM, $P = 0.012$) and a decrease in muscle sympathetic nerve activity (normal sleep versus sleep deprivation = 28 ± 6 versus 22 ± 6 bursts/min, $P = 0.017$). Heart rate, forearm vascular resistance, and plasma catecholamines were not significantly changed by sleep deprivation, nor did sleep deprivation affect autonomic and hemodynamic responses to stressful stimuli. Sleep deprivation results in increased resting blood pressure, decreased muscle sympathetic nerve activity, and no change in heart rate. Thus, the pressor response to sleep deprivation is not mediated by muscle sympathetic vasoconstriction or tachycardia. (*Hypertension*. 2000;35:1173-1175.)

Key Words: sleep deprivation ■ sympathetic nervous system ■ vascular resistance ■ catecholamines

Chronic sleep deprivation affects at least one third of normal American adults.¹ In animal studies, several days of complete sleep deprivation results in an increase in mortality.² It has been suggested that fragmented sleep or sleep deprivation may increase the incidence of cardiovascular events.^{3,4} Cardiovascular events follow a circadian rhythm, with a high incidence of sudden death, myocardial infarction, and stroke in the early morning.⁵⁻⁷

Increases in sympathetic activity, heart rate (HR), and blood pressure (BP) with consequent increased myocardial oxygen demand have been shown to coincide with morning cardiovascular events.⁸⁻¹⁰ Lusardi et al¹¹ noted that in hypertensive patients, sleep deprivation induced increases in BP, HR, and urine norepinephrine on the morning after a night of inadequate sleep. Several studies have proposed the attractive hypothesis that activation of the sympathetic nervous system by sleep deprivation may be implicated in triggering cardiovascular events in the morning hours.¹¹⁻¹³ We are unaware of any direct studies of sympathetic responses to sleep deprivation. We therefore tested the hypothesis that sleep deprivation increases HR, BP, and sympathetic activity and potentiates their responses to stressful stimuli.

Methods

Subjects

We studied 8 healthy subjects (6 men and 2 women age 40 ± 5 years). None of the subjects were taking medications. All subjects abstained

from alcohol and caffeine for 24 hours before each study. Studies were approved by the Institutional Review Board on Human Investigation, and written informed consent was obtained from all subjects.

Protocol

Sleep and Sleep Deprivation Nights

Subjects were asked to spend 2 nights in the Clinical Research Center separated by at least 4 days. During the night, subjects either slept undisturbed or were asked to remain awake for 1 night. The sequence of sleep and sleep deprivation nights was randomized for each subject. Investigators were blinded to whether subjects had undergone a night of sleep or sleep deprivation. The sleep night required that the subject was resting in bed by 11:00 PM and slept without interruption until the next morning. During the sleep deprivation night, subjects were asked to remain awake in bed in the Clinical Research Center throughout the night, to limit their physical activity, and to not eat until morning. Subjects were evaluated by a nurse on both study nights at 15-minute intervals to document whether they were asleep or awake. Subjects remained awake during the night of sleep deprivation; no subjects were observed sleeping. Subjects slept 7.1 ± 0.2 hours during the sleep night. Supine resting BP and venous blood samples were obtained in the morning after each study night. Subjects were given a standard light breakfast before undergoing autonomic and hemodynamic studies.

Study Phase

Subjects were studied in the Human Cardiovascular Physiology Laboratory in the morning immediately after the night of either sleep

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From the Division of Clinical and Administrative Pharmacy (M.K., B.G.P.), College of Pharmacy, and Department of Internal Medicine (G.S., C.A.P.), College of Medicine, University of Iowa, Iowa City, Iowa; Department of Hypertension and Diabetology (K.N.), Medical University of Gdansk, Gdansk, Poland; and Department of Internal Medicine (V.K.S.), Mayo Clinic, Rochester, Minn.

Correspondence to Virend K. Somers, MD, PhD, Department of Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail somers.virend@mayo.edu

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or sleep deprivation. Investigators were blinded to whether subjects had slept or were sleep deprived. Baseline measurements of HR, BP, muscle sympathetic nerve activity (MSNA), and forearm blood flow (FBF) were obtained during 10 minutes of undisturbed supine rest under carefully standardized conditions. The same measurements were then recorded during stress tests. HR was measured continuously by ECG. BP was measured each minute by an automatic sphygmomanometer (Life Stat 200, Physio-Control Corp). MSNA was recorded continuously by obtaining multiunit recordings of postganglionic sympathetic activity to muscle blood vessels, measured from a muscle nerve fascicle in the peroneal nerve posterior to the fibular head as described previously.¹⁴ FBF was measured by venous occlusion plethysmography. Respiration was monitored with a strain-gauge pneumotachometer. Stress tests (sustained handgrip, maximal forearm ischemic response, mental stress, and cold pressor test) were conducted in a randomized manner between sessions with a 15-minute interval between each stressor. The isometric handgrip test was performed by asking the subject to sustain a handgrip of 30% of their maximum voluntary contraction for 2 minutes using a dynamometer. Just before release of the handgrip, an arm cuff was inflated to suprasystolic levels (200 mm Hg) for 2 minutes to evaluate the maximal forearm ischemic response.¹⁵ The mental stress test involved asking the subject to do serial subtractions as fast as possible for 2 minutes. The cold pressor test required subjects to place their hand in ice water for 2 minutes. This test was always performed last because of the sustained effects of the test.

Assays

Plasma catecholamine levels were determined by high-performance liquid chromatography with electrochemical detection.¹⁶ The assay has interassay and intraassay coefficients of variation of 3.4% and 3.1%, respectively, and a lower limit of detection of 25 pg/mL.

Analyses

ECG, FBF, MSNA, and respiration were recorded simultaneously using a computerized data acquisition system (MacLab, AD Instruments) and a Macintosh Quadra 950 Computer (Apple Computer). FBF was measured in milliliters per minute per 100 mL of forearm volume, and forearm vascular resistance (FVR) was calculated as mean arterial pressure divided by FBF and expressed in arbitrary units. For each variable (HR, BP, FBF, and MSNA), every period of data collection was averaged to a single value. Data are mean \pm SEM. Differences in hemodynamics, FVR, MSNA, and plasma catecholamine levels after normal sleep and sleep deprivation were determined with a 2-tailed paired Student's *t* test. Statistical significance was defined as $P < 0.05$.

Results

Baseline Measurements

On the morning after sleep deprivation, resting mean BP was significantly higher (86 ± 2 mm Hg) than on the morning after normal sleep (82 ± 3 mm Hg, $P = 0.012$; Table 1 and the Figure). Systolic BPs were 109 ± 3 and 113 ± 4 mm Hg after sleep and sleep deprivation, respectively ($P = 0.002$). After sleep, diastolic BP was 68 ± 3 mm Hg, compared with 71 ± 2 mm Hg after sleep deprivation ($P = 0.051$). However, MSNA was lower after sleep deprivation (22 ± 2 bursts/min) than after normal sleep (28 ± 2 bursts/min, $P = 0.017$; Figure). HR, FVR, and plasma catecholamine levels were similar after both sleep deprivation and normal sleep.

Responses to Stressors

BP, HR, and MSNA responses to stressful stimuli were unchanged by sleep deprivation (Table 2).

TABLE 1. Comparison of Hemodynamic and Neurohumoral Measurements on the Morning After Sleep and Sleep Deprivation

Measurements	After Normal Sleep	After Sleep Deprivation	<i>P</i>
Systolic BP, mm Hg	109 ± 3	113 ± 4	0.002
Diastolic BP, mm Hg	68 ± 3	71 ± 2	0.051
Mean BP, mm Hg	82 ± 3	86 ± 2	0.012
HR, bpm	62 ± 4	60 ± 4	0.31
FVR, arbitrary units	32 ± 4	38 ± 5	0.16
MSNA, bursts/min	28 ± 2	22 ± 2	0.017
Norepinephrine, pg/mL	146 ± 21	175 ± 25	0.34
Epinephrine, pg/mL	25 ± 3	25 ± 3	0.93

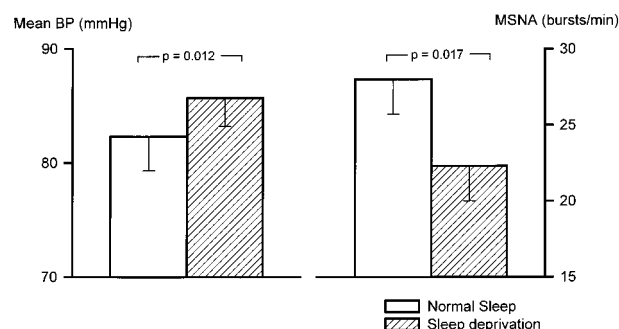
Data are mean \pm SEM.

Discussion

The important and novel findings in our study are, first, that sleep deprivation increases BP but not HR and MSNA and, second, that sleep deprivation does not potentiate cardiovascular responses to stressful stimuli. These data suggest that an increased sympathetic drive is unlikely to be the predominant mechanism mediating an increase in BP after sleep deprivation.

There are surprisingly few controlled studies of the effects of sleep deprivation on neural circulatory control. In prior studies of unmonitored sleep and sleep deprivation, several investigators reported that sleep deprivation increases BP, HR, and urine catecholamine levels.^{11,12} These studies gave rise to the concept that sleep deprivation induced sympathetic activation with consequent increased BP. This hypothesis was based on an increase in urinary excretion of norepinephrine observed during the sleep deprivation night. However, sleep itself is accompanied by decreased sympathetic nerve activity.^{17,18} Urinary catecholamines reflect sympathetic activity over several hours. Thus, urinary catecholamines may represent sympathetic activity during the night of wakefulness and reflect activity patterns rather than heightened activity after sleep deprivation per se. Indeed, in other studies of sleep deprivation, no increases in plasma catecholamines and HR were observed.^{19–21}

Important strengths of our study include, first, the randomized, blinded study design and analysis and, second, that sleep



Group data showing mean BP (left) and MSNA (right) after a night of normal sleep and after a night of sleep deprivation. Sleep deprivation was accompanied by an increase in BP but a decrease in MSNA. Data are mean \pm SEM.

TABLE 2. Changes in Hemodynamic and Sympathetic Nerve Activity During Stressful Stimuli

Measurements	After Normal Sleep	After Sleep Deprivation	P
Δ Mean BP, mm Hg			
SHG	11 \pm 3	13 \pm 2	0.43
MIR	8 \pm 3	11 \pm 3	0.56
MS	2 \pm 1	0 \pm 1	0.07
CPT	12 \pm 3	14 \pm 4	0.71
Δ HR, bpm			
SHG	4 \pm 2	4 \pm 2	1.0
MIR	-1 \pm 1	-2 \pm 1	0.76
MS	3 \pm 2	3 \pm 1	1.0
CPT	4 \pm 2	4 \pm 2	0.86
Δ MSNA amplitude, %			
SHG	33 \pm 12	22 \pm 13	0.11
MIR	33 \pm 12	22 \pm 13	0.60
MS	8 \pm 12	18 \pm 17	0.40
CPT	65 \pm 18	119 \pm 42	0.21

Data are mean \pm SEM. SHG indicates sustained hand grip; MIR, maximal ischemic response; MS, mental stress; and CPT, cold pressor test.

and sleep deprivation were both monitored and documented. Potential limitations of our data include that "normal sleep" was obtained in the hospital environment; this was also true for sleep deprivation. However, this allowed close monitoring and confirmation of either sleep or wakefulness. Subjects in our study were young and healthy. Older subjects and those with cardiovascular disease may be less tolerant of sleep deprivation. Thus, our findings may possibly underestimate the impact of sleep deprivation in older subjects and subjects with those conditions.

Inconsistencies in previous studies of sleep deprivation may be explained in part by the difficulties inherent in ensuring subject compliance with sleep deprivation in an unmonitored situation. Our data show that although sleep deprivation does indeed elicit a modest but significant pressor effect, this pressor response does not appear to be mediated by tachycardia or increases in sympathetic drive. Furthermore, sleep deprivation did not enhance the pressor, chronotropic, or sympathetic responses to mental, physical, or noxious stimuli. Thus, the pressor effect of sleep deprivation appears to be mediated by mechanisms other than enhanced sympathetic vasoconstriction or increased HR.

Possible alternative mediators may include activation of the renin-angiotensin system or enhanced production of the vasoconstrictor endothelin. It is possible that the lower sympathetic activity may be secondary to a baroreflex response to increased BP after sleep deprivation. However, HR was not significantly slower.

In conclusion, although the pressor effect of sleep deprivation may indeed be implicated in any effect of sleep deprivation on cardiovascular events, our data do not support the concept that sleep deprivation may trigger cardiovascular events by increasing sympathetic drive or by potentiating the neural circulatory responses to stressful stimuli.

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