

Total Sleep Deprivation Elevates Blood Pressure Through Arterial Baroreflex Resetting: a Study with Microneurographic Technique

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Study Objectives: Sleep deprivation has a profound effect on cardiovascular regulation through the autonomic nervous system. This study examined the effect of 24-hour total sleep deprivation on muscle sympathetic nerve activity (MSNA), which is a direct measurement of the postganglionic sympathetic efferent innervating the vascular bed in the skeletal muscle and other circulatory structures.

Design: The study was performed on 6 young healthy men. The factors exerting influence on MSNA, such as aging, obesity, body posture, activity, intensity of illumination, and food and beverage consumption were strictly controlled. Burst rate and burst incidence were used as parameters of MSNA. The burst rate, burst incidence, heart rate, and systolic and diastolic blood pressure were measured after total sleep deprivation and control sleep. To perform a linear regression analysis of arterial baroreflex (ABR), the incidence of MSNA bursts corresponding to a given diastolic blood pressure (%MSNA) was examined.

Measurement and Results: The diastolic blood pressure was significantly higher after total sleep deprivation than after control sleep (66.5 ± 1.7 vs 57.4 ± 3.3 mm Hg). The burst rate (9.6 ± 1.8 vs 13.3 ± 2.7 bursts/min) and burst incidence (21.6 ± 4.5 vs 30.3 ± 8.9 bursts/100 heart beats) of MSNA were significantly lower after total sleep deprivation than after control sleep ($P < .05$). Analysis of the ABR disclosed a significant linear regressive relation between %MSNA and diastolic blood pressure in

every subject after both total sleep deprivation and control sleep. This result implies that the ABR regulates the occurrence of MSNA bursts under different diastolic blood pressure conditions. The threshold (X-axis intercept) of the blood pressure regression line (ie, an indicator of the ABR set point) shifted by 12 ± 4.3 mm Hg toward a higher blood pressure level after total sleep deprivation ($P < .05$). The ABR sensitivity, or the slope of the regression line, tended to be less steep after total sleep deprivation than after control sleep, although it was not statistically significant ($P = .09$).

Conclusions: The diastolic blood pressure increased and both burst rate and burst incidence of MSNA decreased after total sleep deprivation. The results show that resetting of the ABR toward a higher blood pressure level occurred after total sleep deprivation. This ABR resetting probably brings about an increase in arterial blood pressure after total sleep deprivation.

Key Words: total sleep deprivation, muscle sympathetic nerve activity (MSNA), arterial baroreflex, resetting, blood pressure, hypertension, autonomic nervous system, angiotensin II, stress, human.

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INTRODUCTION

SLEEP DEPRIVATION HAS A PROFOUND EFFECT ON MANY ASPECTS OF PHYSIOLOGIC FUNCTION, SUCH AS ALERTNESS, COGNITION, MOOD, IMMUNE FUNCTION, AND AUTONOMIC ACTIVITIES. High cardiovascular morbidity is repeatedly reported in shift workers whose sleep is frequently disturbed and insufficient.¹ However, the exact mechanism that causes high cardiovascular morbidity as the result of poor sleep has not been well elucidated. It is quite possible that disrupted sleep has significant influences on the central and peripheral autonomic nervous systems. Recently, muscle sympathetic nerve activity (MSNA), which is a direct record of the activity of the postganglionic sympathetic efferent nerve innervating the vascular bed in the skeletal muscle in man,² is widely accepted as being very informative for the evaluation of sympathetic functions. The change of the burst incidence of MSNA is mainly under the control of the arterial baroreflex (ABR).^{3,4}

In this study, we examined the effect of 24-hour total sleep deprivation (TSD) on heart rate (HR), blood pressure (BP), MSNA, and serologic markers such as catecholamines. There has been only 1 report on MSNA change after TSD: Kato et al⁵ reported that BP elevated and MSNA decreased after TSD; however the exact mechanism for such change is not clear. In order to clarify the mechanism for BP elevation after TSD, we also analyzed the function of the ABR.

METHODS

The subjects consisted of 6 healthy male students (age range, 20 to 28 years). None of them were obese, smokers, or hypertensive. We chose only men to avoid the influence of sex-specific effects. All of the subjects gave informed consent after receiving information about the purpose and risks involved in the present study. The subjects were ordered to stop consuming alcohol for at least 4 days prior to the experiment.

Total Sleep Deprivation

The subjects came to the laboratory at 10:00 PM on the experimental day. After the electrodes for recording the polysomnogram, including electroencephalography and electrocardiography (CM5, NASA), were placed, each subject spent 1 night lying supine in a dark (less than 50 lux), sound-attenuated, and shielded room. To keep the subject awake and to totally deprive his nocturnal sleep, he was allowed to watch video programs on an LED monitor (less than 15 lux at the eye level) and to talk with the other participants in the recording room. Another observer in the neighboring room monitored the polysomnogram and kept the subjects awake by calling their names whenever they became drowsy.

Disclosure Statement

No significant financial interest/other relationship to disclose.

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Procedure

At 8:00 AM after a night of TSD or control sleep (CS), each subject was asked to continue lying in a supine position in bed and empty his urinary bladder. All subjects remained fasting until the experiment was over. Room temperature was kept at 24°C to 25°C. Light intensity was set below 50 lux at the subject's eye level. A tungsten microelectrode for recording MSNA was inserted in the peroneal nerve at the position posterior to the knee as described previously.^{2,3} The BP at the radial artery was continuously recorded by a noninvasive tonometric device (JEN-TOW 7000, Nihon Colin, Japan), as were the MSNA, electrocardiogram, and polysomnogram. All experiments were conducted between 9:00 AM and 11:00 AM. For the control study, the same procedure other than TSD was repeated in every subject at an interval longer than 1 week.

In the control study, subjects again came to the lab at 10:00 PM and were allowed to sleep from 11:00 PM to 7:00 AM the next morning. The order of TSD and CS was randomly assigned in the 6 subjects. The data collection under the TSD and CS conditions in each subject was not repeated, since intraindividual reproducibility of resting human MSNA is reported to be high.^{7,8}

Serologic Markers

Plasma levels of cortisol, norepinephrine, epinephrine, dopamine, glucose, insulin, thyroid stimulating hormone, and glucagon were measured at 11:00 PM and the next morning at 8:00 AM in both the CS and TSD studies.

Data Collection and Analysis

After obtaining a good MSNA signal, we waited 15 minutes for adaptation, and data from the next 15 minutes were used for analysis. Burst rate (BR), which is the number of peaks in the integrated MSNA trace per minute, and burst incidence (BI), which is calculated as the BR per 100 heart beats, were used as parameters of MSNA. The BR, BI, HR, and systolic and diastolic BP (SBP, DBP) after TSD were compared with results after CS with the use of the Wilcoxon signed rank test. Statistical significant level was set at .05.

Sensitivity and the set point of ABR regulation were also analyzed using the same method as Fagius et al.,^{8,9} Wallin et al.,¹⁰ and Kienbaum et al.¹ In brief, all DBPs within more than 300 consecutive heart beats were measured, and, for each diastole, we checked whether or not it was associated with a burst. The DBP of an individual heart beat was grouped in intervals (classes) of 1 mm Hg. The percentage of diastoles associated with a sympathetic burst for each class (%MSNA) was plotted against the DBP, and simple linear regression analysis was performed, with the regression analysis of the data in this experimental condition reaching a significant level ($P < .05$) in each subject. The ABR set point was defined as the DBP intercepting the x-axis of the regression line, and the ABR sensitivity was defined as the slope of the regression line (absolute value). Then, these parameters after TSD and CS were compared with the use of Wilcoxon signed rank test.

RESULTS

The DBP was significantly higher after TSD than after CS (66.5 ± 1.7 mm Hg vs 57.4 ± 3.3 mm Hg, $P = .02$; Figure 1, left panel). The BR of MSNA (9.6 ± 1.8 bursts/min vs 13.3 ± 2.7 bursts/min, $P = .02$; Figure 1, middle panel) and the BI of MSNA (21.6 ± 4.5 bursts/100 heart beats vs 30.3 ± 8.9 bursts/100 heart beats, $P = .04$; Figure

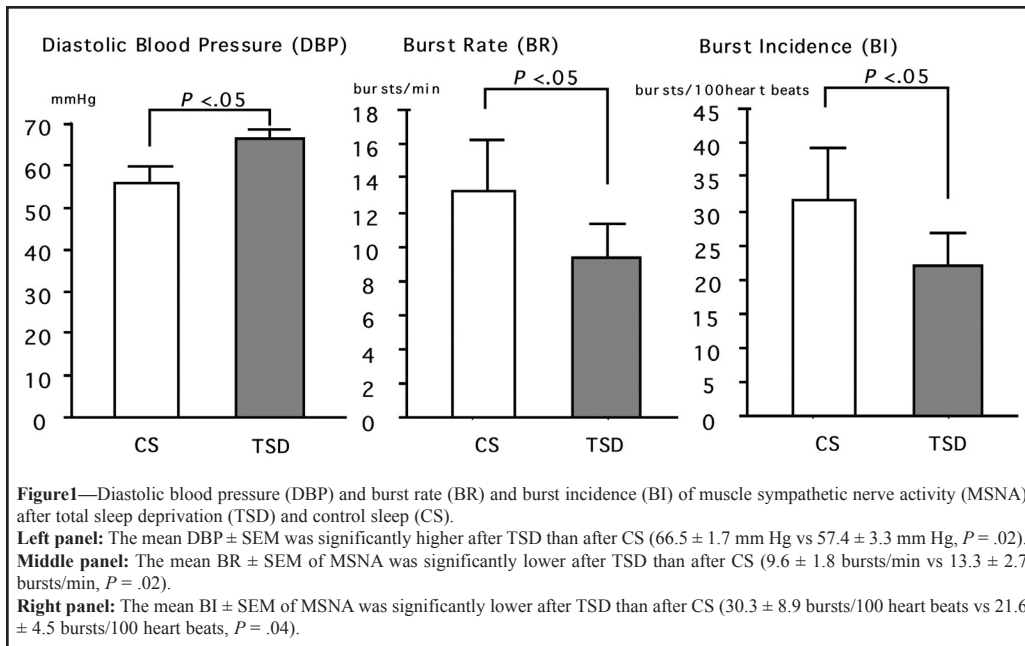


Figure 1—Diastolic blood pressure (DBP) and burst rate (BR) and burst incidence (BI) of muscle sympathetic nerve activity (MSNA) after total sleep deprivation (TSD) and control sleep (CS).
Left panel: The mean DBP ± SEM was significantly higher after TSD than after CS (66.5 ± 1.7 mm Hg vs 57.4 ± 3.3 mm Hg, $P = .02$).
Middle panel: The mean BR ± SEM of MSNA was significantly lower after TSD than after CS (9.6 ± 1.8 bursts/min vs 13.3 ± 2.7 bursts/min, $P = .02$).
Right panel: The mean BI ± SEM of MSNA was significantly lower after TSD than after CS (30.3 ± 8.9 bursts/100 heart beats vs 21.6 ± 4.5 bursts/100 heart beats, $P = .04$).

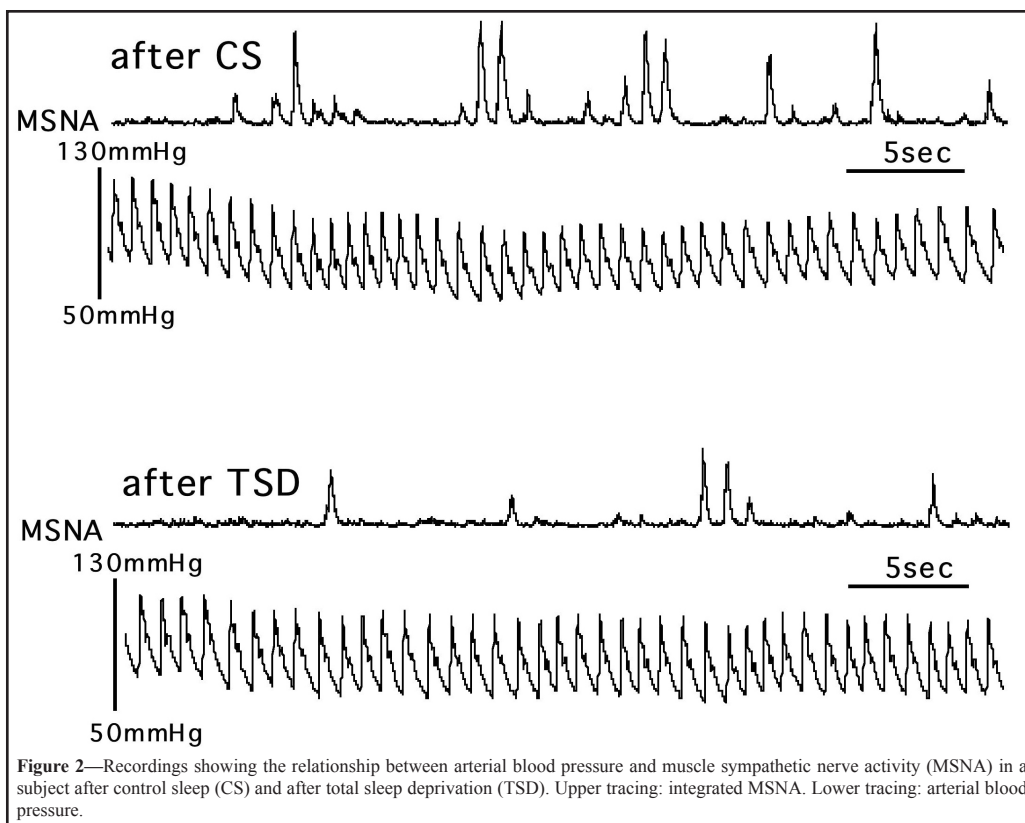


Figure 2—Recordings showing the relationship between arterial blood pressure and muscle sympathetic nerve activity (MSNA) in a subject after control sleep (CS) and after total sleep deprivation (TSD). Upper tracing: integrated MSNA. Lower tracing: arterial blood pressure.

1, right panel) were significantly lower after TSD than after CS. An example of the relationship between BP and MSNA in a subject after CS and after TSD is shown in Figure 2. There were no significant differences in SBP or HR after TSD as compared with after CS.

A statistically significant negative correlation was observed between %MSNA and DBP in every subject, either after TSD or after CS (Table

Table 1—Arterial baroreflex analysis after control sleep and total sleep deprivation in 6 subjects.

Subject	Set Point mm Hg		Sensitivity		Correlation Coefficient, R ² value, %MSNA vs DBP	
	CS	TSD	CS	TSD	CS (P value)	TSD (P value)
1	50.5	59.8	5.6	3.0	0.90 (<.0001)	0.72 (<.002)
2	65.2	75.4	2.7	2.6	0.69 (<.003)	0.77 (<.0001)
3	62.1	71.1	4.4	1.8	0.77 (<.0001)	0.78 (<.0001)
4	82.7	82.9	2.8	3.8	0.64 (<.004)	0.89 (<.0001)
5	70.8	82.0	5.8	4.2	0.86 (<.0001)	0.89 (<.0001)
6	46.2	78.0	3.6	2.2	0.74 (<.003)	0.77 (<.02)
Mean	62.9	74.9	4.2	2.9		
SEM	5.5	3.5	0.6	0.4		

CS refers to control sleep; TSD, total sleep deprivation; DBP, diastolic blood pressure, %MSNA, the incidence of muscle sympathetic nerve activity bursts corresponding to a given DBP

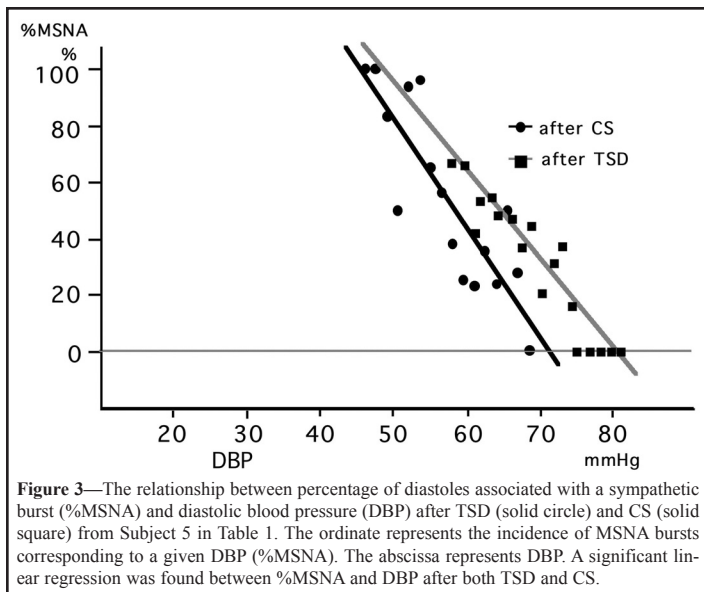


Figure 3—The relationship between percentage of diastoles associated with a sympathetic burst (%MSNA) and diastolic blood pressure (DBP) after TSD (solid circle) and CS (solid square) from Subject 5 in Table 1. The ordinate represents the incidence of MSNA bursts corresponding to a given DBP (%MSNA). The abscissa represents DBP. A significant linear regression was found between %MSNA and DBP after both TSD and CS.

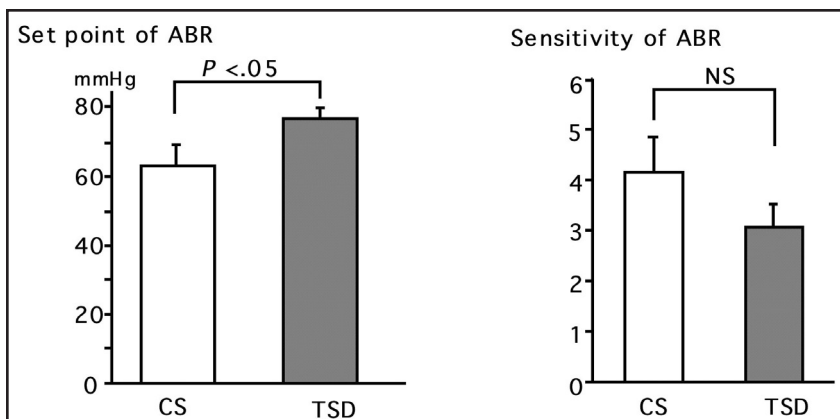


Figure 4—Set point and sensitivity of arterial baroreflex (ABR) after total sleep deprivation (TSD) and after control sleep (CS)

Left panel. Set point of ABR, which is the x-axis intercept, was compared after TSD and CS. The mean set point \pm SEM of the ABR after TSD was significantly higher than after CS (74.9 ± 3.5 mm Hg vs 62.9 ± 5.5 mm Hg, $P = .02$).

Right panel. The ABR sensitivity, which is the slope of ABR (absolute value), after TSD and after CS were compared. The ABR sensitivity of 5 out of 6 subjects was lower after TSD than after CS, although it was not statistically significant (NS) ($P = .09$).

1). Figure 3 shows the result of the analysis in 1 subject (Subject 5 in Table 1). The ABR set point was significantly higher after TSD than after CS (74.9 ± 3.5 mm Hg vs 62.9 ± 5.5 mm Hg, $P = .02$; Figure 4, left panel). The ABR sensitivity in 5 out of 6 subjects was lower after TSD than after CS, although it was not statistically significant ($P = .09$; Figure 4, right panel). Plasma levels of cortisol, norepinephrine, epinephrine, dopamine, glucose, insulin, thyroid stimulating hormone, and glucagon showed no significant difference between TSD and CS study conditions.

DISCUSSION

In the present study, we evaluated the influence of TSD on the activity of the sympathetic nervous system in young healthy men. After TSD, the MSNA significantly decreased and the DBP significantly increased. On the other hand, SBP, HR, and serologic markers (including catecholamines) did not show any significant differences after TSD compared with after CS.

Previous studies that have examined the effect of TSD on cardiovascular function and sympathetic activity have not yet reached a consensus result. Reports describe increases in BP, HR, and urine catecholamine level;¹² no change in BP;¹³ or no change in HR¹⁴ after TSD compared with after CS. However, in all of these studies, wakefulness of the subject during TSD was not monitored, and the subjects were not healthy. In addition, factors such as aging, sex, obesity, body posture, physical activity, intensity of illumination, and food and beverage consumption that exert a significant influence on the sympathetic nervous system were not strictly controlled. Therefore, it is difficult to compare the results of the present study with those of the previous studies.

Prior to conducting the present study, we expected that TSD would enhance sympathetic activity simply because sleep is accompanied by decreased sympathetic activity.¹⁵ However, the study showed that MSNA was reduced and serum catecholamine levels did not change in spite of an elevation in DBP after TSD. Kato et al⁵ reported a similar finding and speculated that the increase in BP was caused not by sympathetic activation of the central nervous system, but by a peripheral mechanism such as an activation of the renin-angiotensin system and an enhanced production of the vasoconstrictor endothelin.

To clarify whether sympathetic activity in the central nervous system changed after TSD, we further analyzed the function of the ABR according to the method by Fagius et al,^{8,9} Wallin et al,¹⁰ and Kienbaum et al,¹¹ as described above. Wallin et al¹⁰ showed that %MSNA had a highly significant and negative correlation to DBP in both normotensive and hypertensive subjects. In the present study, a significant negative correlation was also found between DBP and %MSNA after both TSD and CS in all subjects. This implies that the ABR regulates the occurrence of

MSNA bursts and modifies DBP variability after both TSD and CS conditions. After TSD, the threshold BP (x-axis intercept of the correlation line), which is an indicator of the ABR set point, shifted by about 12 ± 4.3 mm Hg toward a higher BP level. The ABR sensitivity, which is expressed by the slope of the correlation line between DBP and %MSNA, tended to be lower after TSD than after CS (2.9 ± 0.6 vs 4.2 ± 0.4 , mean \pm SEM, $P = .09$). The results showed that ABR resetting toward a higher BP level occurred after TSD.

Kato et al attributed DBP elevation and decreased MSNA after TSD to a peripheral mechanism only; however, our present results indicate that the central mechanism that modifies ABR possibly also affects the DBP and the MSNA change after TSD. We propose that a new equilibrium of cardiovascular regulation under an increased sympathetic neural outflow is achieved through ABR resetting, and excessively raised BP is followed by a reduction in MSNA.

A detailed neural mechanism of ABR resetting is not yet well known, but it is known that the ABR resetting takes place through mental stress.¹⁶ Sleep deprivation is a significant factor that contributes to stress. Therefore, it is possible that the same mechanism as mental stress contributes to the

ABR resetting after TSD. In an animal study, Qian ZM et al¹⁷ reported that ABR resetting toward a higher BP level and reduced ABR sensitivity occurred after a stress load caused by electric shock to the foot in rats, and these effects were reversed by subsequent intracerebroventricular administration of angiotensin-II antagonists. These results suggest that stress-induced ABR resetting is caused through angiotensin-II activation in the central nervous system. Thus, it is possible that ABR resetting by sleep deprivation as well as by stress may be attributed to angiotensin-II activation in the central nervous system. However, our present study did not include a measurement of plasma angiotensin-II. Further study is necessary in this context. The ABR sensitivity tended to be blunted after TSD. It may be a physiologic adaptation to and mitigation of the effect of elevated BP.

One limitation of our present study is the small sample size. To observe the change of ABR sensitivity after TSD, and the sex or age difference, we need to perform further studies with more subjects. The second limitation of our present study is that we saw the effect of acute sleep deprivation over only 1 night. To elucidate the importance of poor sleep on the cardiovascular system, more study of this kind after chronic sleep deprivation is desirable.

In summary, we found that DBP increased and both the BR and BI of MSNA decreased after TSD. Analysis of the ABR function disclosed that baroreflex resetting toward a higher BP level with a tendency to blunt the ABR sensitivity occurred after TSD. Although it is not clear whether this resetting of the ABR is the main cause of BP elevation after TSD, the present results clearly indicate that TSD affects the central sympathetic nervous system. More studies on the effect of both acute and chronic sleep deprivation are needed to clarify the mechanism of health problems caused by poor sleep, which are very common in modern society.

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