

Insomnia With Physiological Hyperarousal Is Associated With Hypertension

Yun Li, Alexandros N. Vgontzas, Julio Fernandez-Mendoza, Edward O. Bixler, Yuanfeng Sun, Junying Zhou, Rong Ren, Tao Li, Xiangdong Tang

Abstract—Previous studies have suggested that insomnia with objective short sleep duration is associated with a higher risk of hypertension, and it has been speculated that the underlying mechanism is physiological hyperarousal. In this study, we tested whether insomnia with physiological hyperarousal measured by Multiple Sleep Latency Test (MSLT), a standard test of sleepiness/alertness, is associated with increased risk of hypertension. Two hundred nineteen chronic insomniacs and 96 normal sleepers were included in this study. Chronic insomnia was defined based on standard diagnostic criteria with symptoms lasting ≥ 6 months. All subjects underwent 1 night in laboratory polysomnography followed by a standard MSLT. We used the median mean MSLT value (ie, >14 minutes) and the 75th percentile of mean MSLT value (ie, >17 minutes) to define hyperarousal. Hypertension was defined based either on blood pressure measures or on diagnosis treatment by a physician. After controlling for age, sex, body mass index, apnea–hypopnea index, diabetes mellitus, smoking, alcohol, and caffeine use, insomnia combined with MSLT >14 minutes increased the odds of hypertension by 300% (odds ratio=3.27; 95% confidence interval=1.20–8.96), whereas insomnia combined with MSLT >17 minutes increased even further the odds of hypertension by 400% (odds ratio=4.33; 95% confidence interval=1.48–12.68) compared with normal sleepers with MSLT ≤ 14 minutes. Insomnia associated with physiological hyperarousal is associated with a significant risk of hypertension. Long MSLT values may be a reliable index of the physiological hyperarousal and biological severity of chronic insomnia. (*Hypertension*. 2015;65:644-650. DOI: 10.1161/HYPERTENSIONAHA.114.04604.) • [Online Data Supplement](#)

Key Words: hypertension ■ insomnia ■ multiple sleep latency test ■ physiological hyperarousal ■ sleep ■ sleep initiation and maintenance disorders

Insomnia is the most prevalent sleep disorder in the general population. Although one fourth to one third of the general population reports a complaint of difficulty in falling or staying asleep,^{1–8} $\approx 10\%$ present chronic complaints and seek medical help for insomnia.^{9,10}

In the past several decades, most studies have focused on the comorbidity of insomnia and psychiatric disorders.^{11,12} However, it is only in the past few years that several studies have reported on the relationship between chronic insomnia and medical morbidity and mortality.^{13–20} In particular, chronic insomnia associated with objective short sleep duration has been linked with higher risk of hypertension, diabetes mellitus, neurocognitive impairment, and mortality.^{18,19,21,22} Furthermore, it was suggested that physiological hyperarousal may be the key mechanism leading to morbidity and mortality in this insomnia phenotype.^{18,19,21,23–25} Several studies have shown that insomnia

is associated with increased resting heart rate,²⁶ impaired heart rate variability,²⁶ higher metabolic rate,²⁷ higher body temperature,²⁸ activation of the hypothalamic–pituitary–adrenal axis,²³ as well as increased β electroencephalograph activity^{29,30} and brain metabolic rate³¹ as compared with normal sleepers, suggesting that insomnia is a disorder of physiological hyperarousal present throughout the 24-hour sleep–wake cycle.

The Multiple Sleep Latency Test (MSLT) is used in clinical practice to measure daytime sleepiness and alertness.³² Lower values indicate excessive daytime sleepiness (eg, sleep latency <8 minutes), whereas higher values suggest hyperalertness. Despite the fact that chronic insomniacs complain of significant daytime fatigue, earlier studies have consistently shown that insomnia is associated with higher MSLT values compared with controls.^{25,33,34} These findings contrast with the results in normal sleepers that after sleep deprivation demonstrate low

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From the Sleep Medicine Center, Mental Health Center, Translational Neuroscience Center, and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, Sichuan, China (Y.L., Y.S., J.Z., R.R., T.L., X.T.) and Department of Psychiatry, Sleep Research and Treatment Center, Pennsylvania State University College of Medicine, Hershey (Y.L., A.N.V., J.F.-M., E.O.B.).

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Correspondence to Xiangdong Tang, Sleep Medicine Center, West China Hospital, Sichuan University, 28 Dian Xin Nan Jie, Chengdu, Sichuan 610041, China. E-mail xiangdong.tang@gmail.com or Alexandros N. Vgontzas, Department of Psychiatry H073, Penn State University College of Medicine, 500 University Dr, Hershey, PA 17033, E-mail avgontzas@psu.edu

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MSLT values.^{35,36} Also, experimental studies have shown that MSLT values are affected by the degree of induced physiological hyperarousal. For example, it has been shown that MSLT is reliably increased in normal young adults and in insomniacs after brief physiological arousal (ie, walking) and the increase in MSLT values is paralleled by increased heart rate.^{37–39} Also, in another study used caffeine in healthy controls, as a model of acute and chronic insomnia, was associated with a significant increase in metabolic rate and MSLT values.⁴⁰ These data suggest that MSLT is a valid measure of physiological arousal.

In this study, our goal is to examine the association between physiological hyperarousal, as measured by the MSLT, and hypertension in chronic insomnia. We hypothesize that there is a significant, dose–response association between different levels of hyperarousal and risk of hypertension.

Methods

Subjects

This was a between-group, cross-sectional, observational study conducted at the Sleep Medicine Center, West China Hospital of Sichuan University, China. Individuals with insomnia and normal sleepers matched for age and sex comprised the study sample. The whole study procedure was approved by the University's Institutional Review Board and informed consent was obtained from each participant.

All patients with insomnia were adults (aged >18 years) and selected consecutively from the Sleep Medicine Center, West China Hospital of Sichuan University between January 2010 and July 2014. Normal sleepers were recruited from college students and their relatives and from the medical and technical staff and visitors of West China Hospital with posted announcements during the same period. A complete medical history and physical examination, including mental status assessment was performed. All potential research subjects were interviewed with a comprehensive questionnaire. The questionnaire provided history of sleep complaints, general health, and medication use. Patients with insomnia met Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR) criteria for primary insomnia.⁴¹ In addition, to ensure the chronicity of their symptoms, the patients with insomnia were also required to report ≥6-month duration of insomnia symptoms instead of 1 month, minimum required by the DSM-IV-TR. The normal sleepers were adults who reported no sleep complaints and had no major medical or psychiatric conditions based on their history and physical examination. We excluded insomnia and normal sleep subjects who had (1) a chronic sleep-disruptive medical condition (eg, pain); (2) a current major psychiatric condition (eg, depression and anxiety disorders); (3) current and past use of hypnotics, anxiolytics, antidepressants, and any other psychotropic medication; (4) evidence of sleep disordered breathing disorder, that is, an apnea–hypopnea index ≥5, (5) evidence of sleep-related movement disorder, that is, a periodic limb movement index ≥15; (6) evidence of a hypersomnia disorder, that is, MSLT ≤8 minutes, ≥2 sleep onset rapid eye movement periods or total score on Epworth Sleepiness Scale >10; and (7) any other comorbid sleep disorder as per sleep interview (eg, restless legs syndrome).

During the January 2010 to July 2014 recruitment period, 844 consecutive insomniacs and 117 normal sleepers were studied in the sleep laboratory. After an overnight polysomnography followed by a standard MSLT study, a total of 315 individuals, 219 insomniacs and 96 normal sleepers met selection criteria for this study. The normal sleeping and insomnia groups were similar in terms of age (39.5±10.8 and 40.0±10.2 years, respectively) and sex (63% and 67% women, respectively). The sampling procedure and the participant flow in the study are available in the online-only Data Supplement.

Polysomnography

All subjects were evaluated for 1 night in the sleep laboratory in sound-attenuated, light- and temperature-controlled rooms. During this evaluation, subjects were allowed to sleep ad libitum based

on their habitual sleep time, with the recording time range from 22:00–23:00 to 6:00–7:00. Subjects were continuously monitored with 16-channel polygraphs, including electroencephalographic, bilateral electrooculography, electromyography, and electrocardiography. All sleep parameters recorded by polysomnography were analyzed and scored according to the international criteria of American Academy of Sleep Medicine⁴² by a senior technician who was blind to any diagnosis.

Multiple Sleep Latency Test

The MSLT was performed on the day immediately after the overnight polysomnography recording and was comprised four 20-minute nap opportunities at intervals of 2 hours (9:00, 11:00, 13:00, and 15:00).⁴³ Subjects were monitored by technical staff between naps to prevent unscheduled sleep episodes. Sleep onset required the presence of any sleep stage for a duration of ≥30 s. If no sleep occurred, the trial was terminated at 20 minutes and a sleep latency of 20 minutes was assigned.

Hypertension

Blood pressure was measured at 2 time points: in the evening ≈2 hours before starting the polysomnography recording (ie, 20:00–21:00) and in the morning after the end of polysomnography recording and before getting up from bed (ie, 06:00–07:00). We used a pneumoelectric microprocessor–controlled instrument with the appropriate-sized cuffs during this study. The accuracy of this monitor is reported to be ±3 mmHg; in addition, internal calibration was performed before each use, and the machine was checked against a mercury sphygmomanometer at least once a year. The recorded blood pressure was the average of 3 consecutive readings during a 5-minute period after ≥10 minutes of rest in the supine position. Hypertension was defined as (1) a diastolic blood pressure ≥90 mmHg or a systolic blood pressure (SBP) ≥140 mmHg at either evening or morning measurement, (2) use of antihypertensive medication, or (3) physician-diagnosis of hypertension as per clinical history.

Other Key Measurements

Subjective daytime sleepiness was measured by Epworth Sleepiness Scale⁴⁴ that subjects completed it during the sleep laboratory visit. To control for potential confounding factors influencing the relationship between insomnia and hypertension, diabetes mellitus was defined as whether subjects were being treated for diabetes mellitus or had a physician-diagnosis of diabetes mellitus as per clinical history. We also ascertained history of tobacco (current or past use of any type of tobacco product), alcohol (>2 alcohol drinks per day), and caffeine use (>2 coffee or tea drinks per day). Body mass index was based on measured height (cm) and weight (kg) during the subjects' sleep laboratory visit.

Statistical Analyses

Data are presented as the mean±SD for continuous variables and frequency and percent for categorical variables. Bivariate comparisons between groups were conducted using the independent-sample *t* test or Mann–Whitney *U* test for normally and not normally distributed continuous variables and using χ^2 test for categorical variables.

Logistic regression was used to assess the independent association of insomnia with hypertension compared with normal sleep. We performed 2 logistic regression models to examine the association of insomnia with hypertension based on different levels of hyperarousal measured by MSLT values. First, we divided samples into 4 groups based on the median MSLT values of the entire study sample: normal sleepers with an MSLT value above the median (ie, >14 minutes), normal sleepers with an MSLT value below the median (ie, ≤14 minutes), insomniacs with an MSLT value above the median (ie, >14 minutes), and the insomniacs with an MSLT value below the median (ie, ≤14 minutes). Second, to test whether there is a dose–response relationship between different levels of hyperarousal and risk of hypertension in chronic insomnia, we examined the association of the group of insomnia with MSLT values

above the 75th percentile (ie, >17 minutes) with hypertension. We used the normal sleepers with MSLT \leq 14 minutes as the common reference group in these analyses. We calculated the odds ratios (ORs) and 95% confidence intervals (95% CI) from these models to estimate the odds of having hypertension associated with insomnia and longer MSLT values as compared with normal sleepers with MSLT \leq 14 minutes. We adjusted for age, sex, body mass index, diabetes mellitus, apnea–hypopnea index, and tobacco, alcohol, and caffeine consumption. Data were analyzed using SPSS version 19.0 (online-only Data Supplement).

Results

The demographic, clinical, and sleep characteristics of the normal sleep and insomnia groups, as well as normal sleep and insomnia subgroups based on different levels of hyperarousal are presented in Table 1. The night-time sleep characteristics and the correlations between MSLT values and night-time sleep in the study subjects are presented in Table S1 Results section of this article.

In Table 2, we present the ORs of hypertension associated with insomnia and normal sleep and insomnia combined with longer MSLT values, whereas simultaneously adjusting for potential confounding factors. Insomnia was associated with a nearly significant increased odds for hypertension compared with normal sleepers (OR=2.17; 95% CI=0.98–4.84). The odds of hypertension were significantly higher in insomniacs with longer MSLT values in a dose–response manner. Compared with normal sleepers with MSLT \leq 14 minutes, insomnia with MSLT >14 minutes was associated with \approx 300% increase in OR (3.27; 95% CI=1.20–8.96), whereas the joint effect of insomnia and MSLT >17 minutes was associated with an increased \approx 400% (OR=4.33; 95% CI=1.48–12.68; Figure 1). In contrast, in insomniacs with MSLT \leq 14 minutes, the odds of hypertension were not significantly increased compared with normal sleepers with MSLT \leq 14 minutes (OR=1.17; 95% CI=0.40–3.43). The odds of hypertension of normal

Table 1. Demographic, Clinical, and Sleep Characteristics of Study Sample

Characteristics	Sleep Difficulty		Normal Sleep		Insomnia	
	Normal Sleep (n=96)	Insomnia (n=219)	MSLT \leq 14 min (n=60)	MSLT>14 min (n=36)	MSLT \leq 14 min (n=108)	MSLT>14 min (n=111)
Demographic and clinical						
Women, n (%)	60 (62.5)	145 (66.5)	38 (63.3)	22 (61.1)	70 (64.8)	75 (67.6)
Age, y	39.55 \pm 10.82	40.00 \pm 10.16	39.63 \pm 10.45	39.42 \pm 11.55	40.25 \pm 9.74	39.75 \pm 10.59
BMI, kg/m ²	22.59 \pm 2.79	22.01 \pm 2.78	22.87 \pm 2.69	22.13 \pm 2.92	22.19 \pm 2.80	21.84 \pm 2.76
Hypertension, n (%)	9 (9.4)	37 (16.9)	6 (10)	3 (8.3)	12 (11.1)	25 (22.5)*
SBP, mm Hg	111.04 \pm 2.82	112.28 \pm 10.62	110.99 \pm 14.02	111.13 \pm 10.72	110.81 \pm 11.08	113.72 \pm 10.00*
DBP, mm Hg	70.48 \pm 7.87	70.57 \pm 7.71	70.28 \pm 8.13	70.81 \pm 7.51	69.00 \pm 7.34	72.10 \pm 7.80†
NM-SBP, mm Hg	109.07 \pm 10.64	111.86 \pm 10.38*	108.47 \pm 11.10	110.03 \pm 9.95	110.67 \pm 11.09	113.06 \pm 9.51
NM-DBP, mm Hg	69.28 \pm 6.77	70.22 \pm 7.47	68.84 \pm 6.77	69.99 \pm 6.82	68.87 \pm 7.18	71.57 \pm 7.55†
Diabetes mellitus, n (%)	1 (1.0)	2 (0.9)	1 (1.7)	0 (0)	1 (0.9)	1 (0.9)
Tobacco, n (%)	7 (7.3)	24 (11.0)	4 (6.7)	3 (8.3)	12 (11.1)	12 (10.8)
Alcohol, n (%)	7 (7.3)	20 (9.1)	5 (8.3)	2 (5.6)	9 (8.3)	11 (9.9)
Caffeine, n (%)	11 (11.5)	18 (8.2)	7 (11.7)	4 (11.1)	8 (7.4)	10 (9.0)
Daytime alertness						
ESS	4.73 \pm 3.15	2.57 \pm 2.92 ‡	4.82 \pm 3.30	4.58 \pm 2.94	3.05 \pm 3.14	2.10 \pm 2.62*
MSLT, min	13.06 \pm 3.13	14.29 \pm 3.40 †	11.06 \pm 1.86	16.38 \pm 1.63‡	11.30 \pm 1.61	17.20 \pm 1.77‡
9:00 nap, min	13.79 \pm 6.26	13.61 \pm 6.64	11.12 \pm 6.08	18.25 \pm 3.38‡	9.31 \pm 5.91	17.79 \pm 4.20‡
11:00 nap, min	12.93 \pm 6.02	14.05 \pm 5.97	10.85 \pm 5.71	16.40 \pm 4.86‡	11.57 \pm 6.03	16.46 \pm 4.84‡
13:00 nap, min	11.68 \pm 6.63	13.78 \pm 6.11*	9.88 \pm 6.42	14.69 \pm 5.91‡	10.97 \pm 5.90	16.52 \pm 4.99‡
15:00 nap, min	13.41 \pm 5.97	15.68 \pm 5.88†	11.82 \pm 6.00	16.06 \pm 4.94‡	13.29 \pm 6.54	18.01 \pm 3.99‡

Comparisons between normal sleep and insomnia groups, within normal sleep and insomnia subgroups. BMI indicates body mass index; DBP, diastolic blood pressure, mean diastolic blood pressure taken in the evening and in the morning; ESS, Epworth Sleepiness Scale; MSLT, Multiple Sleep Latency Test; NM-DBP, diastolic blood pressure in subjects not on antihypertensive medication; NM-SBP, systolic blood pressure in subjects not on antihypertensive medication; and SBP, systolic blood pressure, mean systolic blood pressure taken in the evening and in the morning.

* P <0.05, † P <0.01, ‡ P <0.001.

Table 2. Multivariable Adjusted Odds Ratios (95% CI) of Hypertension Associated With Insomnia and Different Levels of Physiological Hyperarousal

Predictors	n	Adjusted OR	95% CI	
Normal sleep	96	1.00	Low	Upper
Insomnia	219	2.17	0.98	4.84
Normal sleep				
MSLT ≤ 14 min	60	1.00		
MSLT > 14 min	36	0.87	0.19	3.90
Insomnia				
MSLT ≤ 14 min	108	1.17	0.40	3.43
MSLT > 14 min	111	3.27	1.20	8.96
MSLT > 17 min	54	4.33	1.48	12.68

All data adjusted for sex, age, apnea–hypopnea index, body mass index, diabetes mellitus, tobacco, alcohol, and caffeine use. CI indicates confidence interval; MSLT, Multiple Sleep Latency Test; and OR, odds ratio.

sleepers with MSLT >14 minutes were not significantly increased compared with normal sleepers with MSLT ≤14 minutes (OR=0.87; 95% CI=0.19–3.90). Furthermore, we examined the association of insomnia with hypertension but not on antihypertensive medication based on different levels of mean MSLT values. The results remained significant and in the same direction (online-only Data Supplement). In Figure 2, we present the observed dose–response association between MSLT values and frequency of hypertension, as well as mean blood pressure levels in insomniacs. Even after excluding the participants who were using antihypertensive medication, the linear relationship between blood pressure and MSLT values was still significant (SBP, P -linear=0.04; diastolic blood pressure, P -linear=0.003). The data in normal sleepers are now presented in Figure S1.

Discussion

This is the first study to demonstrate that insomnia with physiological hyperarousal, as measured by MSLT, is associated with a significant risk for hypertension in a dose–response manner. This increased risk is independent of comorbid

conditions frequently associated with insomnia or hypertension, such as age, sex, body mass index, diabetes mellitus, apnea–hypopnea index, alcohol, tobacco, and caffeine use, as well as depression, anxiety, or other comorbid sleep disorders. Furthermore, our findings suggest that long mean MSLT values may be a useful marker of the biological severity and medical effect of insomnia.

Until a few years ago, the association of insomnia with hypertension was inconsistent and modest.^{13,15} However, in recent years, studies using objective measures of sleep demonstrated a significant association between insomnia and hypertension.^{18,21} Lanfranchi et al⁴⁵ reported that night-time SBP was higher and day-to-night SBP dipping was lower in insomniacs compared with controls and that the magnitude of β electroencephalograph activity correlated with SBP dipping in insomniacs. Vgontzas et al²¹ assessed the joint effect of insomnia and objective short sleep duration on hypertension risk in the general population (ie, Penn State Adult Cohort) and found that compared with normal sleepers with sleep duration >6 hours, the highest odds of hypertension was in insomniacs with <5 hours of sleep duration (OR=5.1) and the second highest in insomniacs who slept 5 to 6 hours (OR=3.5). More recently, longitudinal data from the Penn State Adult Cohort showed that insomniacs with objective short sleep duration have a significantly higher risk of incident hypertension,¹⁸ suggesting that it is insomnia that causes hypertension and not vice versa.

In this study, we used MSLT values as a direct measure of physiological hyperarousal.³⁹ Insomnia with mean MSLT values >14 or >17 minutes had ≈300% and 400% higher odds of hypertension, respectively, than normal sleepers with MSLT ≤14 minutes. In contrast, insomniacs whose mean MSLT values were ≤14 minutes did not show increased odds for hypertension compared with normal sleepers with MSLT ≤14 minutes. Thus, the observed dose–response pattern in the association of MSLT values with hypertension strengthens our view that physiological hyperarousal is directly associated with the risk of cardiovascular morbidity and mortality in insomniacs.

Traditionally, insomnia has been perceived primarily as a night-time sleep disorder and most treatments, pharmacological and nonpharmacological, aim at improving night-time

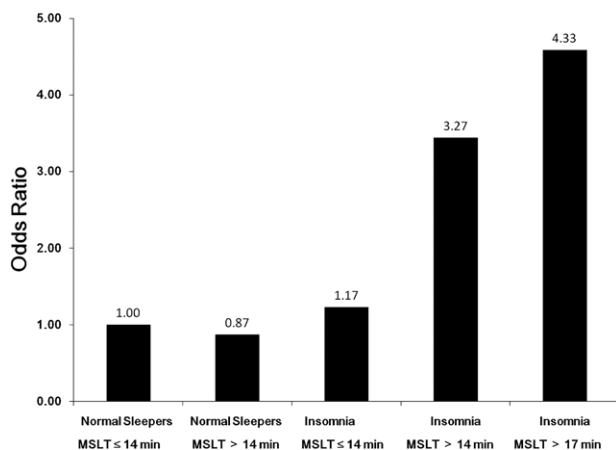


Figure 1. Multivariable adjusted odds ratios of hypertension associated with insomnia and different levels of physiological hyperarousal. All data adjusted for sex, age, apnea–hypopnea index, body mass index, diabetes mellitus, tobacco, alcohol, and caffeine use. MSLT indicates Multiple Sleep Latency Test.

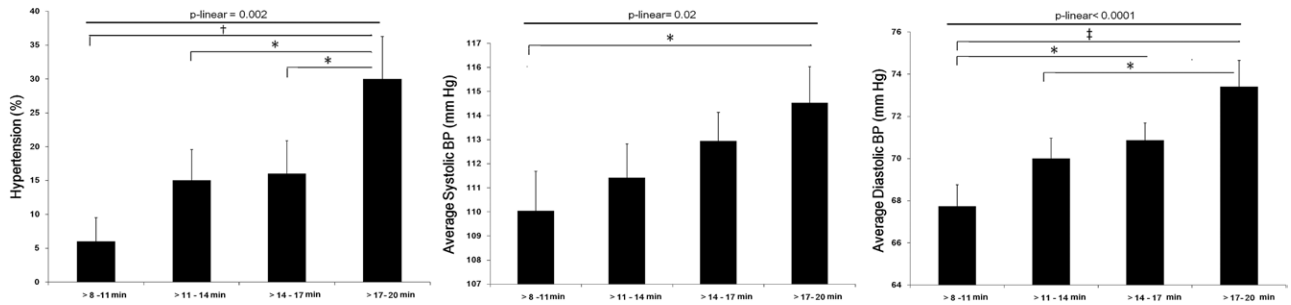


Figure 2. Frequency of hypertension and mean blood pressure across different levels of physiological hyperarousal in patients with insomnia. Average systolic BP: mean systolic blood pressure taken in the evening and in the morning; Average diastolic BP: mean diastolic blood pressure taken in the evening and in the morning. MSLT indicates Multiple Sleep Latency Test. * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$.

sleep. However, several studies have suggested that insomnia is a state of 24-hour hyperarousal rather than a state of night-time hypervigilance.^{12,22–24,46} This study provides further support to the 24-hour hyperarousal model for chronic insomnia, and suggests that our intervention should aim at reducing the overall emotional and physiological hyperarousal and its underlying mechanisms present throughout the 24-hour sleep–wake period.

According to American Academy of Sleep Medicine guidelines,⁴³ polysomnography and MSLT are not routinely recommended for evaluation in insomnia. The findings of this study suggest that MSLT measurement may provide an alternative to objective short sleep duration as a reliable index of the biological and medical significance and severity of insomnia. However, because MSLT, which is conducted in the sleep laboratory, is rather costly and impractical, other simpler methods, such as pupillometry⁴⁷ or measures of peripheral sympathetic activation, need to be tested and validated for measuring physiological hyperarousal. In our study, subjective measurement of sleepiness, that is, Epworth Sleepiness Scale, did not predict risk of hypertension in patients with insomnia. Thus, it seems that subjective methods of sleepiness/alertness could not replace MSLT and that the 2 methods most probably measure different central nervous system functions.

Our data on the association of insomnia with long MSLT values with hypertension support the previously proposed phenotyping of insomnia.³¹ One phenotype, the more biologically severe type of insomnia, is associated with 24-hour physiological hyperarousal and significant cardiometabolic sequelae, for example, hypertension. The other phenotype, a less biologically severe form of insomnia, is not associated with physiological hyperarousal or significant cardiometabolic morbidity. These 2 phenotypes may respond differentially to treatment approaches; for example, the first phenotype may respond better to treatments, such as medication or biofeedback therapy to reduce physiological hyperarousal, whereas the second phenotype may benefit from cognitive behavioral therapy to modify sleep-related cognitions, emotions, and behaviors. This hypothesis should be tested in future clinical trials.

There are several strengths of this study, such as its large sample size, its careful ascertainment of the subjects and that our measurements were not confounded by the use of sleep and other psychotropic medication or presence of other frequent

sleep and mental disorders. However, there are some limitations in this study that need to be acknowledged. First, the polysomnography recording was ad libitum, which may explain the stronger association found between MSLT in insomnia subgroups and sleep efficiency as compared with sleep duration. Second, the results in this study were based on 1 night of polysomnography recording, which may not be representative of the subjects' habitual sleep and may not capture the severity of insomnia. However, in our previous studies, the association between objective sleep duration and hypercortisolemia was based on a 4 consecutive night sleep laboratory protocol, which should represent the typical sleep profile of the subjects better.^{23,24} Interestingly, in a preliminary study of short- and long-term stability on sleep measures, we found that total sleep time, sleep latency, and wake after sleep onset were moderately to substantially stable >3 or 4 subsequent nights or 2.5 years after in both insomniacs and controls.^{48,49} Third, our study is cross-sectional and cannot provide causality in terms of the direction of the association. However, consistently with a previous longitudinal study on incident hypertension,¹⁸ it is unlikely that hypertension can induce long MSLT values. Finally, we did not perform blood pressure measurements before and after MSLT, which would have allowed a temporally closer examination of the association between these 2 variables.

Perspectives

In summary, insomnia with long MSLT values is associated with a high risk for hypertension. Long MSLT values may be a reliable index of the biological and medical severity of insomnia and of the degree of 24-hour physiological hyperarousal in patients with insomnia. It seems that the reduction of this 24-hour hyperarousal should be our therapeutic goal and not just improvement of night-time sleep.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Although physiological hyperarousal has been proposed as the primary mechanism that connects insomnia with cardiovascular disease, this study is the first to test this hypothesis directly by using a standard measure of hyperarousal, such as the Multiple Sleep Latency Test.

What Is Relevant?

- Insomnia is highly prevalent in the outpatient practice of general practitioners, such as family doctors, internists, and cardiologists. Severe chronic insomnia is associated with increased risk of hypertension. Physicians should become aware that patients with hypertension might have untreated severe chronic insomnia.

Summary

Insomnia combined with physiological hyperarousal is associated with a high risk of hypertension. Given the high prevalence of insomnia in the general population, its early diagnosis and appropriate management should become a target of public health policy in the prevention of cardiovascular disease.

Insomnia With Physiological Hyperarousal Is Associated With Hypertension

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ONLINE DATA SUPPLEMENTS

INSOMNIA WITH PHYSIOLOGICAL HYPERAROUSAL IS ASSOCIATED WITH HYPERTENSION

Yun Li, MD;^{1,2} Alexandros N. Vgontzas, MD;² Julio Fernandez-Mendoza, PhD;² Edward O.

Bixler, PhD;² Yuanfeng Sun, MD;¹ Junying Zhou, MD;¹ Rong Ren, MD,¹ Tao Li, MD;¹

Xiangdong Tang, MD, PhD¹

Short title: Insomnia, Hyperarousal, and Hypertension

1. Sleep Medicine Center, Mental Health Center, Translational Neuroscience Center, and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China
2. Sleep Research & Treatment Center, Department of Psychiatry, Pennsylvania State University College of Medicine, Hershey, PA

ONLINE SUPPLEMENTAL METHODS

Subjects

This was a between-groups, cross-sectional, observational study conducted at the Sleep Medicine Center, West China Hospital of Sichuan University, China. Individuals with insomnia and normal sleepers matched for age and gender comprised the study sample. This study was approved by the Research Ethics Board of the West China Hospital of Sichuan University and informed consent was obtained from each participant.

All insomniacs were adults (age > 18 years) and selected consecutively from the Sleep Medicine Center, West China Hospital of Sichuan University between January 2010 and July 2014. Normal sleepers were recruited from college students and their relatives and from the medical and technical staffs and visitors of West China Hospital with posted announcements during the same period. A complete medical history and physical examination including mental status assessment was performed. All potential research subjects were interviewed with a comprehensive questionnaire. The questionnaire provided history of sleep complaints, general health and medication use. Patients with insomnia met Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR) criteria for primary insomnia.¹ In addition, in order to ensure the chronicity of their symptoms, the insomniacs were also required to report at least 6-month duration of insomnia symptoms instead of 1-month minimum required by the DSM-IV-TR. The normal sleepers were adults who reported no sleep complaints and had no major medical or psychiatric conditions based on history and physical examination. We excluded insomnia and normal sleep subjects who had (1) a chronic sleep-disruptive medical condition (e.g., pain); (2) a current major psychiatric condition (e.g., depression and anxiety disorders); (3) current and past use of hypnotics, anxiolytics, antidepressants, and any other psychotropic medication; (4) evidence of sleep disordered breathing disorder, i.e., an apnea-hypopnea index (AHI) ≥ 5 , (5) evidence of sleep-related movement disorder, i.e., a periodic limb movement index (PLMI) ≥ 15 ; (6) evidence of a hypersomnia disorder, i.e., MSLT ≤ 8 min, ≥ 2 sleep onset rapid eye movement periods (SOREMPs) and/or total score on Epworth Sleepiness Scale (ESS) > 10 ; and (7) any other co-morbid sleep disorder as per sleep interview (e.g., restless legs syndrome).

During the January 2010 to July 2014 recruitment period, 844 consecutive insomniacs and 117 normal sleepers were studied in our sleep laboratory. After an overnight PSG followed by a standard MSLT study, 54.2% insomniacs (n = 457) were excluded based on current and past use of medication, 18.0% insomniacs (n = 152) and 11.1% normal sleepers (n = 13) were excluded based on AHI ≥ 5 , 0.2% insomniacs (n = 2) and 0.9% normal sleepers (n = 1) were excluded based on PLMI ≥ 15 , as well as 1.7% insomniacs (n = 14) and 6.0% normal sleepers (n = 7) were

excluded based on $MSLT \leq 8$ min, ≥ 2 SOREMPs and/or total score on ESS > 10 . A total of 315 individuals, 219 insomniacs and 96 normal sleepers met selection criteria for the present study. The normal sleeping and insomnia groups were similar in terms of age (39.5 ± 10.8 and 40.0 ± 10.2 years, respectively) and gender (63% and 67% female, respectively).

Polysomnography

All subjects were evaluated for one night in the sleep laboratory in sound-attenuated, light- and temperature-controlled rooms. During this evaluation, subjects were allowed to sleep ad libitum based on their habitual sleep time, with the majority of the subjects recorded from 22:00-23:00 to 6:00-7:00. Overnight PSG recording techniques and standard parameters were performed according to the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events². Sleep data were collected and scored via the Alice 5 Diagnostic Sleep System (Philips Respironics, Bend, OR, USA). Subjects were continuously monitored with 16-channel polygraphs including electroencephalographic, bilateral electrooculography, electromyography and electrocardiography. Respiration was monitored throughout the night with oronasal thermocouples, nasal pressure transducer and thoracic/abdominal strain gauges. All-night recordings of hemoglobin oxygen saturation (SpO_2) were obtained with an oximeter attached to the finger. All sleep parameters recorded by PSG were analyzed according to the international criteria of AASM² by a senior technician who was blind to any diagnosis. Sleep continuity parameters, assessed from the sleep recordings, included: sleep onset latency (SOL), wake after sleep onset (WASO), total sleep time (TST), time in bed (TIB), and sleep efficiency ($TST / TIB * 100$). Sleep onset latency was defined as the latency from lights out to the first occurrence of any stage of sleep for a duration of 1 minute or longer; if, however, the initial stage of sleep was stage 1, then it had to be followed without any interfering wakefulness, by at least 1 minute of any other stage. In addition, standard sleep architecture parameters were evaluated, including percent of time asleep spent in stages 1, 2, 3 (slow wave sleep) and rapid eye movement (REM) sleep.

Multiple sleep latency test

The MSLT was performed on the day immediately after the overnight PSG recording and was comprised of four 20-min nap opportunities at intervals of 2 hours (9:00, 11:00, 13:00 and 15:00).³ Subjects were monitored by a technical staff between naps to prevent unscheduled sleep episodes. Sleep onset required the presence of any sleep stage for a duration of 30 sec or longer. If no sleep occurred, the trial was

terminated at 20 min and a sleep latency of 20 min was assigned. The mean sleep latency was the average sleep latency from all four naps.

Hypertension

Blood pressure was measured at two time points: in the evening about 2 hours before starting the PSG recording (i.e., 20:00-21:00) and in the morning after the end of PSG recording and before getting up from bed (i.e., 06:00-07:00). We used a pneumoelectric microprocessor-controlled instrument with the appropriate sized cuffs during this study. The accuracy of this monitor is reported to be ± 3 mm Hg; in addition, internal calibration was performed before each use, and the machine was checked against a mercury sphygmomanometer at least once a year. The recorded blood pressure was the average of 3 consecutive readings during a 5-min period following at least 10 min of rest in the supine position. Hypertension was defined as (1) a diastolic blood pressure ≥ 90 mm Hg and/or a systolic blood pressure ≥ 140 mm Hg at either evening or morning measurement, (2) use of antihypertensive medication, or (3) physician-diagnosis of hypertension as per clinical history.

Other key measurements

Subjective daytime sleepiness was measured by ESS⁴ that subjects completed it during the sleep laboratory visit. To control for potential confounding factors influencing the relationship between insomnia and hypertension, diabetes was defined as whether subjects were being treated for diabetes or had a physician-diagnosis of diabetes as per clinical history. We also ascertained history of tobacco (current or past use of any type of tobacco product) and alcohol (> 2 alcohol drinks per day), and caffeine use (> 2 coffee or tea drinks per day). Body mass index (BMI) was based on measured height (cm) and weight (kg) during the subjects' sleep laboratory visit.

Statistical analyses

Data are presented as the mean \pm standard deviation (SD) for continuous variables and frequency and percent for categorical variables. Bivariate comparisons between groups were conducted using the independent-sample t-test or Mann–Whitney U-test for normally and not normally distributed continuous variables and using Chi-square test for categorical variables. Pearson correlation was used to examine the correlation between MSLT values and nocturnal sleep parameters.

Logistic regression was used to assess the independent association of insomnia with hypertension compared to normal sleep. We performed two logistic regression models to examine the association of insomnia with hypertension based on different

levels of hyperarousal measured by MSLT values. First, we divided samples into four groups based on the median MSLT values of the entire study sample: normal sleepers with a MSLT value above the median (i.e., > 14 min), normal sleepers with a MSLT value below the median (i.e., ≤ 14 min), insomniacs with a MSLT value above the median (i.e., > 14 min) and the insomniacs with a MSLT value below the median (i.e., ≤ 14 min). Second, in order to test whether there is a dose-response relationship between different levels of hyperarousal and risk of hypertension in chronic insomnia, we examined the association of the group of insomnia with MSLT values above the 75th percentile (i.e., > 17 min) with hypertension. We used the normal sleepers with MSLT ≤ 14 min as the common reference group in these analyses. We calculated the odds ratios and 95% confidence intervals (95% CI) from these models to estimate the odds of having hypertension associated with insomnia and longer MSLT values as compared to normal sleepers with MSLT ≤ 14 min. We adjusted for age, gender, BMI, diabetes, AHI, and tobacco, alcohol, and caffeine consumption. Data were analyzed using SPSS version 19.0.

ONELINE SUPPLEMENTAL RESULTS

Independent Association of Insomnia with Hypertension Based on Different Levels of Hyperarousal Measured by Nocturnal Objective Sleep

The correlations between MSLT and nocturnal PSG derived sleep latency (Pearson $r = 0.13$, $p = 0.02$), sleep duration (Pearson $r = -0.21$, $p < 0.0001$), WASO (Pearson $r = 0.23$, $p < 0.0001$) and sleep efficiency (Pearson $r = -0.27$, $p < 0.0001$) were significant.

After adjusting for confounding factors, insomnia combined with longer nocturnal sleep latency > 12.5 min (the median of nocturnal sleep latency of the total study subjects) increased the odds of hypertension by 250% (OR= 2.78, 95% CI= 1.04-7.44) whereas insomnia combined with even longer nocturnal sleep latency > 23.5 min (the 75th percentile of nocturnal sleep latency of the total study subjects) increased even further the odds of hypertension by 350% (OR= 3.77, 95% CI= 1.29-11.02) compared to normal sleepers with nocturnal sleep latency ≤ 12.5 min.

After adjusting for confounding factors, insomnia combined with shorter sleep duration < 6 h (the 25th percentile of sleep duration of the total study subjects) increased the odds of hypertension by 350% (OR= 3.49, 95% CI= 1.16-10.50) whereas insomnia combined with even shorter sleep duration < 5 h (the 12.5th percentile of TST of the total study subjects) increased even further the odds of hypertension by 380% (OR= 3.82, 95% CI= 1.04-14.00) compared to insomniacs with sleep duration ≥ 6 h. However, we used normal sleepers with TST ≥ 7 h (the median

of TST of the total study subjects) as the reference control, the risk of hypertension was increased in insomniacs with shorter sleep duration (sleep duration < 7 h, OR= 2.02, 95% CI= 0.73-5.56 and sleep duration < 6 h, OR=2.12, 95% CI= 0.69-6.54) but without significances. This difference did not reach significance due to the ad libitum PSG protocol and the fact that insomniacs stayed in bed longer than controls.

After adjusting for confounding factors, insomnia combined with WASO > 1h (the median of WASO of the total study subjects) increased the odds of hypertension by 370% (OR= 3.72, 95% CI= 1.56-11.95) whereas insomnia combined with WASO > 1.8 h (the 75th percentile of WASO of the total study subjects) increased even further the odds of hypertension by 470% (OR= 4.65, 95% CI= 1.35-15.94) compared to normal sleepers with WASO ≤ 1 h.

Because the PSG recording was ad libitum, which may explain the stronger association found between MSLT in insomnia subgroups and sleep efficiency as compared to sleep duration. After adjusting for confounding factors, insomnia combined with lower sleep efficiency < 84% (the median of sleep efficiency of the total study subjects) increased the odds of hypertension by 300% (OR= 3.18, 95% CI= 1.03-9.88) whereas insomnia combined with even lower sleep efficiency < 73% (the 25th percentile of sleep efficiency of the total study subjects) increased even further the odds of hypertension by 400% (OR= 4.10, 95% CI= 1.21-13.87) compared to normal sleepers with sleep efficiency ≥ 84%.

We analyzed the data including the subjects with high blood pressure but not taking antihypertensive medication. Because there was only one subject with hypertension in normal sleepers by only blood pressure measurements, we performed logistic regression analysis only within insomniacs and used the insomniacs with MSLT ≤ 14 min as the reference group. After adjusting for confounding factors, insomnia combined with MSLT > 14 min increased the odds of hypertension by 250% (OR= 2.54, 95% CI= 1.09-5.94) whereas insomnia combined with MSLT > 17 increased even further the odds of hypertension by 400% (OR= 3.97, 95% CI= 1.57-10.03) compared to insomnia with MSLT ≤ 14 min. These results remained significant and similar to those obtained when we included in the analysis all hypertensive subjects with and without antihypertensive medication.

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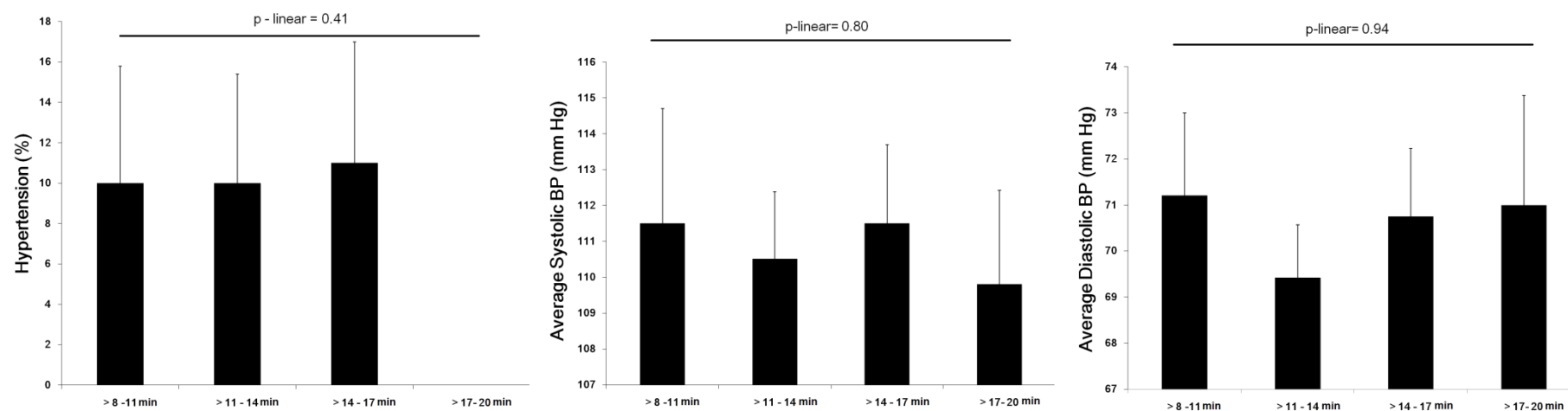


Figure S1. Frequency of hypertension and mean blood pressure across different levels of physiological hyperarousal in normal sleepers. MSLT: Multiple Sleep Latency Test; BP: Blood Pressure; Average systolic BP: mean systolic blood pressure taken in the evening and in the morning; Average diastolic BP: mean diastolic blood pressure taken in the evening and in the morning.

Table S1. Nighttime sleep Characteristics of Study Sample

Characteristics of nighttime Sleep	Sleep Difficulty		Normal Sleep		Insomnia	
	Normal Sleep (n = 96)	Insomnia (n = 219)	MSLT ≤ 14 min (n = 60)	MSLT > 14min (n = 36)	MSLT ≤ 14min (n = 108)	MSLT >14min (n = 111)
Total Time in Bed (min)	497.35 ± 50.17	508.16±43.83*	498.15 ± 48.87	496.03 ±52.96	506.21 ± 44.28	510.06 ± 43.51
Sleep Onset Latency (min)	17.89 ± 22.70	23.05 ± 26.18	15.34 ± 18.46	23.13 ± 28.18	20.90 ± 25.70	25.13 ± 26.59
WASO (min)	61.75 ± 52.31	84.91 ± 63.22‡	52.49 ± 45.24	77.18 ± 59.88*	76.25 ± 58.08	93.33 ± 67.05*
Total Sleep Time (min)	413.20 ± 76.76	400.21 ± 77.10	429.99 ± 65.83	385.21± 86.01*	409.06 ± 69.80	391.60 ± 83.01
Sleep Efficiency (%)	83.08 ± 13.26	78.77 ± 13.63*	86.33 ± 10.52	77.66 ± 15.56‡	80.86 ± 12.09	76.73 ± 14.75*
N1 (%TST)	15.22 ± 7.49	17.82 ± 11.47*	15.33 ± 7.40	15.03 ± 7.75	18.11 ± 9.18	17.53 ± 13.36
N2 (%TST)	49.76 ± 9.64	52.00 ± 11.65	50.30 ± 9.59	48.86 ± 9.80	50.92 ± 11.18	53.05 ± 12.04
N3 (%TST)	16.32 ± 7.21	13.09 ± 7.28‡	15.62 ± 7.33	17.48 ± 6.94	13.47 ± 6.94	12.71 ± 7.60
R (%TST)	18.70 ± 4.48	17.09 ± 6.54*	18.74 ± 4.14	18.64 ± 5.05	17.49 ± 6.87	16.70 ± 6.22
AHI (events/h)	1.18 ± 1.21	1.20 ± 1.24	1.18 ± 1.23	1.19 ± 1.20	1.32 ± 1.24	1.09 ± 1.24

WASO, Wake after Sleep Onset; AHI, Apnea Hypopnea Index. Comparisons between normal sleep and insomnia groups, within normal sleep and insomnia subgroups, * P < 0.05, † P < 0.01, ‡ P < 0.001

生理性过度觉醒相关失眠与高血压相关

Insomnia With Physiological Hyperarousal Is Associated With Hypertension

Yun Li, Alexandros N. Vgontzas, Julio Fernandez-Mendoza, Edward O. Bixler, Yuanfeng Sun, Junying Zhou, Rong Ren, Tao Li, Xiangdong Tang

苏国海 译

既往研究提示客观睡眠时间缩短的失眠者具有更高的高血压患病风险，并推测其潜在的机制在于生理性的过度觉醒。在本研究中，我们采用睡眠/觉醒标准测试法，即多次睡眠潜伏期试验（Multiple Sleep Latency Test, MSLT）来测试生理性过度觉醒相关失眠是否与高血压风险增加有关。本研究纳入了219例慢性失眠患者及96名正常人。慢性失眠的标准诊断为失眠症状持续 ≥ 6 个月。所有受试者都用实验多导睡眠图来进行标准的MSLT，并监测一夜。我们把超过MSLT平均中位数值（即 > 14 分钟），及MSLT平均值75%分位数（即 > 17 分钟）定义为过度觉醒。并用血压测量或专科医师的诊断来定义高血压。在控制了年龄、性别、体重指数、呼吸暂停-低通气指数、糖尿病、吸烟、饮酒及应用咖啡因等因素后，我们发现失眠并MSLT > 14 分钟的受试者患高血压的几率增加300%（OR=3.27；95%可信区间：1.2~8.96），相较而言，失眠并MSLT > 17 分钟的受试者患高血压的几率甚至高达400%（OR=4.33；95%可信区间：1.48~12.68）。综上所述，生理性过度觉醒相关失眠与高血压风险有显著相关性。另外，MSLT值增高可能是评估生理性过度觉醒及慢性失眠生物学严重程度的一个可靠的指标。

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