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Assessment of sympathetic neural activity in chronic insomnia: evidence for elevated cardiovascular risk FREE

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Abstract

Study Objectives

Chronic insomnia affects up to 15 per cent of adults. Recent cross-sectional and prospective epidemiological studies report an association between insomnia and hypertension, including incident hypertension, yet mechanisms underlying the association remain unknown. We hypothesized that participants with chronic insomnia would have elevated sympathetic neural outflow, blunted baroreflex sensitivity, and augmented sympathetic neural and cardiovascular reactivity to stress when compared with good-sleeper controls.

Methods

Twelve participants with chronic insomnia (11 women, 1 man) and 12 controls (8 women, 4 men) underwent one night of laboratory polysomnography, two weeks of at-home wrist actigraphy, and one night of controlled laboratory sleep prior to a comprehensive morning autonomic function test. The autonomic function test consisted of simultaneous recordings of muscle sympathetic nerve activity (MSNA; microneurography), beat-to-beat blood pressure (finger plethysmography), and heart rate (electrocardiogram) during a 10 min supine baseline and a 2 min cold pressor test.

Results

Baseline blood pressure, heart rate, and MSNA were not different between groups, but sympathetic baroreflex sensitivity was significantly blunted in participants with insomnia (−2.1 ± 1.0 vs. −4.3 ± 1.3 bursts/100 heartbeats/mm Hg; $p < 0.001$). During the cold pressor test, systolic arterial pressure reactivity (Δ21 ± 11 vs. Δ14 ± 8 mm Hg; time × group = 0.04) and total MSNA reactivity (Δ127%, 54%–208% vs. Δ52%, 30%–81%; time × group = 0.02) were augmented in chronic insomnia.

Conclusions

Participants with chronic insomnia demonstrated impaired sympathetic baroreflex function and augmented neural cardiovascular responsiveness to stress, when compared with controls. These findings support growing evidence of cardiovascular risk and physiological hyperarousal in chronic insomnia.

Clinical Trial Registration

NCT02048878. https://clinicaltrials.gov/ct2/show/NCT02048878

primary insomnia, hyperarousal, sympathetic nervous system, baroreflex, hypertension, sleep disorder

Statement of Significance

There is growing evidence that chronic insomnia is associated with heightened risk of hypertension, and that alterations in the sympathetic nervous system contribute to this risk. The present study employed a gold-standard approach to *directly* record muscle sympathetic neural activity in participants with chronic insomnia and healthy controls. Chronic insomnia was associated with impaired sympathetic baroreflex function and heightened sympathetic reactivity to stress when compared with habitual good sleeper controls. Future work should determine whether pharmacological and/or behavioral treatments for insomnia improve sympathetic neural control in patients with chronic insomnia. Our findings provide novel mechanistic insight into the reported associations between chronic insomnia and heightened cardiovascular risk.

Introduction

Chronic insomnia is the most prevalent sleep disorder in the world, affecting up to 15 per cent of adults [1–3]. Recent epidemiological studies have reported significant associations between chronic insomnia and the risk of cardiovascular disease, particularly incident hypertension [4–6]. The putative mechanisms underlying these associations have not been elucidated, but sympathetic overactivity and/or arterial baroreflex dysfunction are suspected targets.

Numerous studies have reported elevated heart rate, increased metabolic rate, increased cortisol and norepinephrine concentrations, and elevated body temperature in patients with chronic insomnia. Taken together, this constellation of abnormalities is consistent with a state of physiological hyperarousal [7, 8]. A common mechanism underlying all of these physiological disruptions is the sympathetic nervous system. Although a number of studies have suggested sympathetic overactivity in chronic insomnia via noninvasive estimates such as heart rate variability (HRV) [9, 10] and impedance cardiography [11–13], a recent review questioned the validity of HRV measures to assess sympathetic activity in chronic insomnia [14].

Microneurography is the only available technique to *directly* record sympathetic neural activity in humans. The approach allows real-time recording of post-ganglionic sympathetic neural activity to the vascular bed of skeletal muscle, commonly referred to as muscle sympathetic nerve activity (MSNA), and is widely acknowledged as the gold-standard assessment for sympathetic neural activity in humans [15, 16]. Concurrent recording of MSNA, electrocardiography, and beat-to-beat blood pressure (BP) via finger plethysmography allow for detailed analysis of the arterial baroreflex, a classic negative-feedback mechanism that contributes to both short- and long-term homeostatic regulations of BP [17].

Consistent with the concept of physiological hyperarousal of insomnia [7, 8], we tested the hypothesis that patients with insomnia would demonstrate (1) elevated sympathetic neural outflow, (2) blunted baroreflex sensitivity (BRS), and (3) augmented sympathetic neural and cardiovascular reactivity to a highly reproducible stressor [18] when compared with good sleeper controls.

Methods

Participants

Participants with chronic insomnia were recruited by study investigators using advertisements posted in the Sleep Disorders and Primary Care Clinics at the University of Chicago and in the community, whereas good sleeper control participants were recruited from the community using flyers and advertisements. Inclusion criteria for all participants were age of 21–65 years and body mass index of <35 kg/m^2. Participants with chronic insomnia were required to meet DSM-V criteria for Insomnia Disorder, Persistent (>3 months) based on the report of symptoms at the time of the screening. We utilized the Insomnia Severity Index (ISI) > 14 arbitrary units (i.e. moderate-to-severe insomnia) and Pittsburgh Sleep Quality Index (PSQI) > 5 arbitrary units to verify severity at the time of screening. The final inclusion criteria for the insomnia group were a self-reported habitual sleep duration of <6.5 hr. Inclusion criteria specific to good sleeper controls included the following: (1) ISI ≤ 7 arbitrary units, (2) PSQI ≤ 5 arbitrary units, and (3) self-reported habitual sleep duration of >6.5 hr and <9 hr. Exclusion criteria for both groups included the following: (1) sleep disorders other

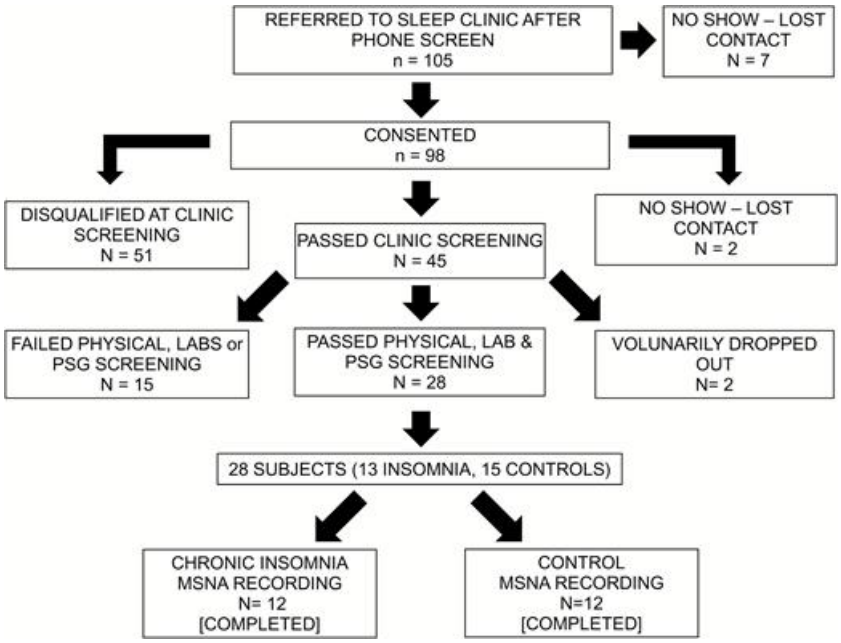
than insomnia as assessed by screening polysomnography (PSG, including an apnea–hypopnea index [AHI] of ≥10 episodes per hour and periodic limb movement arousal index of ≥5 episodes per hour); (2) circadian rhythm sleep disorders; (3) diabetes based on hemoglobin A1c (HbA1c) ≥ 6.5% (for those with HbA1c ≥ 6.0 but <6.5%, the nondiabetic condition was confirmed by 2 hr oral glucose tolerance test); (4) history of meeting DSM-IVR criteria of major psychiatric disorder; (5) unstable or serious medical conditions; (6) current, or use within past month, of psychoactive (other than stable treatment with antidepressant), hypnotic, stimulant, or analgesic medication (except occasional nonnarcotic analgesics), β blockers, or α blockers; (7) shift work or other types of self-imposed irregular sleep schedules; (8) habitual smoking (six or more cigarettes per week); (9) habitual alcohol consumption (more than two alcoholic drinks per day); and (10) pregnancy.

Screening procedures started with a phone screen performed by the professional subject recruiter of the Sleep, Metabolism and Health Center using a written script. Items addressed in the phone screen included contact information, age, sex, height, weight, race, currently used prescription and nonprescription medications, health status, use of stimulants, alcohol, nicotine and recreational drugs, occupation, habitual sleep habits, habitual work habits (shift versus no-shift worker), and pregnancy status for women. For potential participants with insomnia, the script included questions about age at diagnosis, chronicity of insomnia, and treatments. The responses were recorded in writing and provided to the investigators. Between January 2014 and December 2016, 105 potential participants who were eligible based on the phone screen were invited to the clinic screening, which was performed by a clinical psychologist with specialty training and certification in behavioral sleep medicine (L.M.). Seven participants were lost to contact. Thus, 98 potential participants came to the Behavioral Sleep Medicine Clinic, gave informed consent and underwent a 1 hr interview with the Behavioral Sleep Medicine Specialist (L.M.) who conducted a Structured Clinical Interview for DSM disorders (SCID) based on DSM-IV TR, reviewed and scored self-administered questionnaires, and administered the Epworth Sleepiness Scale (participants are asked their chance of dozing in eight different circumstances; scores above 10 suggest clinically significant sleepiness) [19].

Each participant completed the following questionnaires: (1) The Beck Anxiety Inventory (21 symptoms of anxiety are rated on a scale of 0–3; total scores of 0–21 suggest very low anxiety, 22–35 suggest moderate anxiety, and above 36 suggest high anxiety), (2) Center for Epidemiologic Studies Depression Scale (CES-D) (20-item scale where participants rate depressive symptoms on a scale of 0–3 and scores above 16 suggest clinically significant depression), (3) Insomnia Severity Index (7-items pertaining to distress and functional impact of insomnia where participants use 0–4 point ratings and questions pertain to the last 2 weeks), (4) Dysfunctional Beliefs and Attitudes about Sleep Scale (16-item Scale where dysfunctional sleep statements are rated on a scale of 1–10, where 1 is strongly disagree and 10 is strongly agree) [20], (5) Pittsburg Sleep Quality Index (PSQI) (9-item scale including sleep schedule questions and ratings of 0–4 pertaining to sleep quality; component-based global scores above 5 suggest concerns regarding sleep quality), and (6) Perceived Stress Scale (participants rate their degree of stress in the past month by rating their distress response to 14-items as 0–4, where 0 is never and 4 is very often) [21]. The Behavioral Sleep Medicine Specialist then conferred with the principal investigator and co-investigators to determine the participant's eligibility.

A total of 59 participants successfully passed the psychological screening and were scheduled for a screening PSG and other physical/laboratory tests required for study inclusion. A total of 28 participants (13 insomnia and 15 controls) were enrolled and initiated the study, which consisted of 14 days of at-home wrist actigraphy and a morning autonomic function test that included microneurography to directly assess sympathetic neural activity. Per a priori estimates of statistical power, study recruitment, and enrollment continued until microneurographic recordings were successfully obtained in 12 participants with insomnia and 12 controls. A consort diagram is shown in Figure 1.

Figure 1.



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Study consort diagram. Consort diagram depicting how the a priori goal of *n* = 12 participants with chronic insomnia and *n* = 12 habitual good sleeper controls with successful microneurographic recordings was achieved.

There were no changes in any of the participants' medication regimen during the study. One participant with insomnia carried a diagnosis of hypertension and was on a stable dose of hydrochlorothiazide. Results were analyzed with and without this individual, and findings were not different. The University of Chicago Institutional Review Board approved this study, and all participants provided written informed consent prior to participation.

Laboratory PSG and 2 week actigraphy

Each participant underwent one night of in-laboratory PSG for screening purposes. Bedtimes were from 10:00 pm–12:00 am until 7:00 am–9:00 am based on the participants' habitual bedtimes. Each PSG included a minimum of 8 hr of recording. PSG (Nihon Kohden, Foothill Ranch, CA) included recordings of six electroencephalographic channels, bilateral electro-oculograms, chin and tibialis electromyogram, electrocardiogram, airflow by nasal pressure transducer and oronasal thermocouples, chest and abdominal wall motion by respiratory inductance plethysmography belts, and oxygen saturation by finger pulse oximeter. All PSGs were staged and scored according to the 2007 American Academy of Sleep Medicine Manual for the Scoring of Sleep and Related Events [22]. Apneas were defined as a reduction of airflow of at least 90 per cent on the oronasal thermistor for at least 10 s (obstructive if respiratory effort was present and central if respiratory effort was absent). Hypopneas were scored if the magnitude of the signal decreased by at least 30 per cent of the baseline amplitude of the nasal pressure transducer for at least 10 s, and were associated with a 3 per cent or greater drop in oxygen saturation as measured by finger pulse oximetry and/or cortical microarousal. Total AHI was defined as the number of apneas and hypopneas per hour of sleep, and those with AHI of >10 episodes per hour were excluded from the study.

Upon successful completion of the laboratory PSG screen, participants completed 2 weeks of wrist actigraphy (Actiwatch Spectrum Pro, Philips Respironics, Murrysville, PA) to assess habitual sleep duration and quality. Variables of interest from the actigraphy included total sleep time, wake after sleep onset (WASO), and sleep efficiency.

Neural and cardiovascular assessments

Blood pressure and heart rate

Two separates techniques were used to obtain measurements of arterial BP. First, supine resting arterial BPs were measured three consecutive times (separated by ~1 min intervals) using an automated sphygmomanometer (Omron HEM-907XL, Omron Health Care) before and after the 10 min baseline. Second, beat-to-beat arterial BP was recorded continuously using a Portapres system (Finapres Medical Systems, Amsterdam, The Netherlands). All beat-to-beat BP recordings were continuously monitored for quality using standard procedures for operation (i.e. arm at heart level, consistent calibrations, etc.). Arterial BPs were expressed as follows: systolic arterial BP (SAP), diastolic arterial BP (DAP), and mean arterial BP

(MAP); HR was recorded continuously via a three-lead electrocardiogram.

Microneurography

Multifiber recordings of MSNA were obtained by inserting a tungsten microelectrode (FHC, Bowdoin, ME) into the peroneal nerve of the right leg, whereas a reference electrode was inserted 2–3 cm subcutaneously from the recording electrode. Both electrodes were connected to a differential preamplifier and then to an amplifier (total gain of 80000) where the nerve signal was band-pass filtered (700–2000 Hz) and integrated (time constant 0.1). Recordings of MSNA were required to be spontaneous, pulse-synchronous bursts that increased during end-expiratory apnea and remain unchanged during auditory stimulus or stroking of the skin.

Baroreflex sensitivity

Spontaneous sympathetic and cardiovagal BRS were calculated using the WinCPRS program as previously described by our laboratory [23]. Sympathetic BRS was assessed using the slope of the linear relationship between MSNA and DAP during spontaneous baseline breathing. The DAP of individual cardiac cycles was grouped in 3 mm Hg bins (intervals) during baseline. Within these bins, burst incidence was determined and plotted against the corresponding DAP bins. All sympathetic BRS slopes were $r \geq 0.5$.

Cardiovagal BRS was determined from the slope of the relationship between spontaneous changes in R-R interval (RRI) and SAP. Baroreflex sequences were identified as three or more beats of progressive SAP changes and corresponding changes of RRI (lag 1). The criteria for a sequence were set at a minimum of 1 mm Hg for SAP and 4 ms for RRI. BRS during progressive increases in SAP (up-up) and progressive decreases in SAP (down-down) is reported.

Morning autonomic function test

All participants reported to the sleep laboratory the evening prior to the morning autonomic function test. Participants were only instrumented with wrist actigraphy to minimize discomfort and any unintended experimental sleep loss due to PSG. Participants were provided an 8–9 hr opportunity for sleep (10–11 pm lights out) and were woken by study investigators at 7 am for experimental instrumentation (i.e. microneurography, electrocardiogram, and continuous BP). Upon completion of microneurography instrumentation (maximum search time of 45 min), participants were provided 10 min period of quiet rest. During this time, we obtained brachial BPs for Portapres calibration. Following this short period of rest, a 10 min supine baseline was recorded. After the 10 min supine baseline, the Portapres was recalibrated and we recorded a new 3 min baseline, 2 min cold pressor test, and a 3 min recovery. The cold pressor test consisted of submersion of the participants' hand for the full 2 min into an ice bucket (1–3°C). This classic sympathoexcitatory maneuver has been detailed by Victor et al. [24].

Data analysis

All data (e.g. MSNA, beat-to-beat BP, and ECG) were imported and analyzed in the WinCPRS software program (Absolute Aliens, Turku, Finland). R-waves were detected and marked in the time series. Bursts of MSNA were automatically detected on the basis of amplitude with the use of a signal-to-noise ratio of 3:1, within a 0.5 s search window centered on a 1.3 s expected burst peak latency from the previous R-wave. Potential bursts were displayed and edited by one trained investigator. MSNA was expressed as burst frequency (number of burst of activity per minute), burst incidence (number of burst of activity per 100 heart beats), and total MSNA (total number of bursts multiplied by the averaged normalized burst area or amplitude). Total MSNA was analyzed using area and amplitude normalization procedures, and findings were not different.

Sample size calculation

In the a priori power analysis, we used a standard deviation of MSNA = 5.8 (which represents typical standard deviation in our laboratory over the past 12 years) and a maximum effect size of 6. Using $n = 12$ for each group, the estimated power to observe a difference between chronic insomnia vs. controls is 0.813. The MSNA reactivity test using contrasts of treatment means has low variance due to the strong within participant correlation ($r \geq 0.80$). For a change from baseline to response to the cold pressor test of 4.0 units, which we regard as a conservative effect, $n = 12$ participants per group have a power of ≥ 0.80.

Statistical analysis

Assumption of normality was tested for each outcome of interest. When data were normally distributed, variables were compared using the independent *t*-test (insomnia vs. control) and reported as mean ± standard deviation. When assumptions of normality were violated, variables were compared using the nonparametric Wilcoxon test and reported as median (25th–75th percentile). Proportion of objective short sleepers (i.e. <6.5 hr per night) were compared using chi-square test. The Cohen's d was used to estimate effect size for significant differences between the two groups for variables that were normally distributed. All data were statistically analyzed using commercial software (SPSS 22.0, IBM SPSS, Armonk, NY). A *p*-value of <0.05 was considered statistically significant.

Results

Participant characteristics

Age (37 ± 14 vs. 41 ± 15 years, $p = 0.42$), body mass index (BMI, 26 ± 6 vs. 25 ± 4 kg/m^2, $p = 0.51$), and sex distribution (67% vs. 92% female, $p = 0.13$) were not different between groups. Race/ethnicity distributions were not different between participants with insomnia (10 non-Hispanic White, 1 African American, 1 Hispanic) and good sleeper controls (11 non-Hispanic White, 1 African American). All participants with chronic insomnia had an insomnia severity index in the range of moderate to severe (Table 1). Consistent with previous studies, participants with chronic insomnia had higher depressive symptoms, anxiety, dysfunctional beliefs and attitudes about sleep, and lower self-reported sleep quality (Table 1).

Table 1.

Subjective sleep, psychological screening, and objective sleep via one-night laboratory PSG and 2 week at-home wrist actigraphy

Variable	Control (*n* = 12)	Insomnia (*n* = 12)	*P*
Subjective sleep and psychological screen			
Insomnia Severity Index	1 (1–2.5)	20 (17–24)	**<0.001**
Pittsburg Sleep Quality Index	2 (1–4)	13 (11–14)	**<0.001**
Dysfunctional Beliefs/Attitudes About Sleep	61 ± 16	100 ± 27	**<0.001**
Beck Anxiety Inventory	3 (2–7)	11 (7–16)	**0.02**
Center for Epidemiological Study Depression	2 (1–5)	15 (6–26)	**0.001**
Epworth Sleepiness Scale	4 (3–5)	9 (2–12)	0.19
Perceived Stress Scale	34 ± 3	33 ± 4	0.81
Objective sleep via one-night laboratory PSG			
Total sleep time (min)	406 (380–442)	417 (357–429)	0.49
Sleep efficiency (%)	85 ± 8	83 ± 7	0.58
Wake after sleep onset (min)	59 ± 43	62 ± 38	0.86
Apnea–hypopnea index (episodes/hr)	1.9 (0.5–6.1)	4.7 (0.1–6.7)	0.73
Objective sleep via 2 week wrist actigraphy			
Total sleep time (min)	422 (409–439)	379 (301–428)	0.08
Sleep efficiency (%)	90 (86–91)	86 (81–88)	**0.01**
Wake after sleep onset (min)	30 ± 3	41 ± 3	**0.02**
Short sleepers of <6.5 hr/night (%)	8	64	**<0.01**

n = 11 for insomnia actigraphy due to failure of one participant to complete the 2 week actigraphy. Data presented as mean ± standard

deviation (normal distribution) or median (25th–75th percentile) if nonparametric test was required.

Significant *P*-values (*P* <0.05) are bold.

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Laboratory PSG and 2 week actigraphy

Laboratory PSG assessments of sleep duration and quality were not different between groups (Table 1). In contrast, 2 week at-home wrist actigraphy revealed that participants with insomnia were more likely to have habitual sleep duration of <6.5 hr, had significantly lower sleep efficiency, significantly higher WASO, and tended to have lower total sleep time ($p = 0.08$) when compared with controls (Table 1). The mean difference in WASO between the two groups corrsponded to a large effect size, with a Cohen's d of 3.7 times the pooled standard deviation.

Baseline autonomic function

Table 2 depicts sympathetic neural activity and hemodynamics at baseline. Resting BP, HR, and MSNA were not statistically different between groups. Figure 2 depicts that baseline sympathetic BRS was significantly blunted in participants with insomnia (−2.1 ± 1.0 bursts/100 heartbeats/mm Hg) compared with controls (−4.3 ± 1.3 bursts/100 heartbeats/mm Hg; $p < 0.001$). This represents a large effect size of insomnia versus good sleep since Cohen's d was 1.90 times the pooled standard deviation. DAP-MSNA slopes were significantly lower in participants with insomnia ($r = 0.86 \pm 0.14$) when compared with controls ($r = 0.97 \pm 0.03$; $p = 0.02$), but all 24 participants were above the $r = 0.5$ minimum required for analysis. Ascending and descending cardiovagal BRS were not different between groups (Table 2).

Table 2.

Sympathetic neural and hemodynamic measurements during 10 min supine baseline and 2 min cold pressor test

Variable	Control (*n* = 12)	Insomnia (*n* = 12)	*P*
Baseline autonomic function test			
Systolic blood pressure (mm Hg)	113 ± 16	111 ± 19	0.72
Diastolic blood pressure (mm Hg)	67 ± 7	69 ± 10	0.60
Heart rate (beats/min)	60 ± 10	65 ± 10	0.21
MSNA (bursts/min)	25 ± 9	23 ± 11	0.64
MSNA (bursts/100 hb)	41 ± 14	35 ± 17	0.35
Cardiovagal BRS up-up (units)	15 (9–20)	20 (10–27)	0.60
Cardiovagal BRS down-down (units)	16 (11–24)	18 (11–35)	0.54
Cold pressor reactivity test			
ΔSystolic blood pressure (mm Hg)	14 ± 8	21 ± 11	**0.04**
ΔDiastolic blood pressure (mm Hg)	10 ± 4	14 ± 7	0.08
ΔHeart rate (beats/min)	10 ± 10	11 ± 7	0.25
ΔMSNA burst frequency (bursts/min)	9 ± 5	12 ± 11	0.33
ΔMSNA burst incidence (bursts/100hb)	9 ± 11	10 ± 14	0.40
ΔTotal MSNA amplitude (%)	52 (30–81)	127 (54–208)	**0.02**
ΔTotal MSNA amplitude (a.u.)	47 (33–67)	82 (53–115)	**0.01**
ΔTotal MSNA area (%)	46 (28–97)	161 (64–239)	**0.03**
ΔTotal MSNA area (a.u.)	3203 (1887–3990)	5671 (3346–10440)	**0.02**

MSNA = muscle sympathetic nerve activity; BRS = baroreflex sensitivity.

n = 11 controls and *n* = 11 insomnia for cardiovagal BRS. Data presented as mean ± standard deviation (normal distribution) or median (25th–75th percentile) if nonparametric test was required.

Significant *P*-values (*P* <0.05) are bold.

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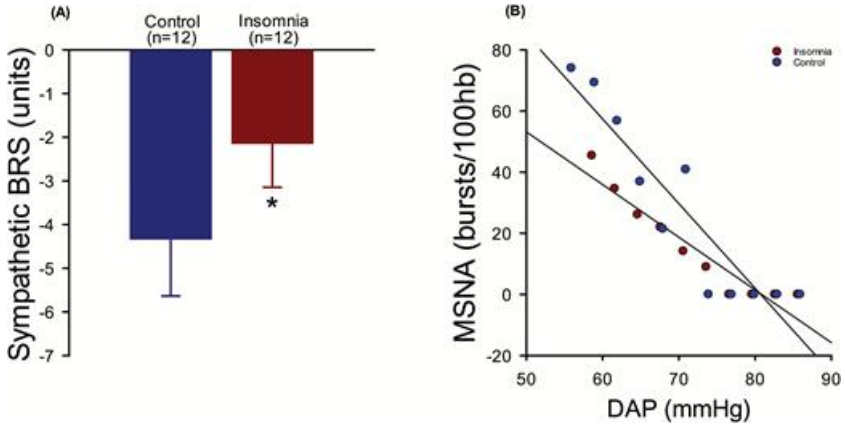
Figure 2.



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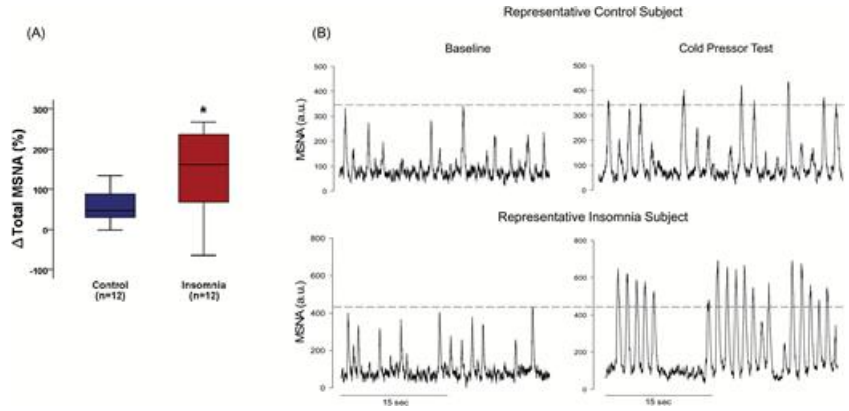
Sympathetic BRS in patients with insomnia. (A) Sympathetic BRS was significantly lower in patients with insomnia compared with controls. Data represented as mean ± standard error; *$p < 0.05$ vs. controls. (B) Representative slope analyses for one insomniac and one control. DAP = diastolic arterial pressure; MSNA = muscle sympathetic nerve activity.

Cold pressor test

Table 2 demonstrates that SAP reactivity to cold pressor test (CPT) was elevated in participants with insomnia compared with controls. A similar trend was present for diastolic BP reactivity, whereas HR reactivity was similar between groups (Table 2). Although changes in MSNA burst frequency and incidence were not different between groups (Table 2), participants with insomnia demonstrated significantly higher total MSNA response to CPT (Figure 3A). The augmented total MSNA reactivity was present when analyzed as percent change or absolute change, as well as when the data were normalized by amplitude or area (Table 2). Figure 3B depicts representative neurograms from an insomnia and control participant during baseline and CPT.

Figure 3.



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Cardiovascular and sympathetic neural reactivity in patients with insomnia. (A) Total MSNA responsiveness to the cold pressor test was significantly higher in patients with chronic insomnia compared with controls. Data expressed as a box-and-whisker diagram. The line in the box represents the median and the box represents the interquartile range (IQR; the difference between 25th and 75th percentile). The upper whisker represents the 75th percentile plus 1.5 times the IQR, whereas the lower whisker represents the 25th percentile minus 1.5 times the IQR. Any value beyond the whiskers was defined as an outlier and not graphed. *$p < 0.05$ vs. controls. (B) Representative microneurographic recordings from a good sleeper control (top) and a participant with chronic insomnia (bottom). Exposure to the cold pressor test increased the number of bursts (i.e. burst frequency/incidence) in both groups, but the increased amplitude/area of those bursts was significantly higher in patients with chronic insomnia. Dotted line represents amplitude normalization to the highest sympathetic burst during baseline condition. Results were similar when total MSNA was normalized by amplitude or area (Table 2).

Discussion

The sympathetic nervous system is a primary modulator of cardiovascular control. We employed microneurography to directly record sympathetic neural activity to the vascular bed of skeletal muscle in participants with chronic insomnia and healthy controls. Microneurographic assessments of peripheral sympathetic nerve activity have been shown to be (1) significantly correlated with cardiac [25] and renal [26] norepinephrine spillover measured via sophisticated radiolabeled infusion and sampling techniques and (2) highly reproducible within an individual [18, 27–29]. Three novel findings are reported in the present study. First, sympathetic baroreflex function was impaired in participants with chronic insomnia. Second, chronic insomnia was associated with an augmented pressor response. Third, the augmented pressor response coincided with a near doubling of MSNA reactivity to blood vessels in the lower leg. The sympathetic baroreflex dysfunction and sympathetic neural hyper-reactivity associated with chronic insomnia provide novel mechanistic insight into the associations between chronic insomnia and heightened cardiovascular risk.

The baroreflex has long been recognized as a key regulator of short-term BP and orthostasis with an important role in long-term control of BP. Baroreflex dysfunction is now widely acknowledged as a key contributor to hypertension [30, 31]. The markedly blunted sympathetic BRS observed in the present study provides not only a viable mechanism to explain the reported link between insomnia and hypertension [4–6], but also a target for prevention and treatment. Although these cross-sectional differences in baroreflex function are significant and have a large effect size, the clinical

impact remains unclear. Future longitudinal studies examining baroreflex function in chronic insomnia participants, particularly after cognitive behavioral therapy for insomnia (CBT-I) and/or pharmacological interventions, appear warranted.

Since the late 1960s, numerous studies have reported physiological hyperarousal in "poor sleepers," and over the past 20 years there have been a number of studies that have extended this concept to carefully selected individuals with clinically diagnosed chronic insomnia [7, 8]. With regard to sympathetic hyperarousal, Bonnet and Arand [9] first reported an increased low-to-high frequency ratio of HRV analyzed via spectral power during wake and all sleep stages in chronic insomnia compared with control, and suggested that this represented heightened sympathetic activity. Since the original findings of Bonnet and Arand [9], there have been a series of reports on HRV in patients with chronic primary insomnia. A recent and comprehensive review by Dodds et al. [14] demonstrates a clear lack of consistent HRV findings within insomnia studies and suggests that there is no, at present, sufficient evidence to support sympathetic hyperarousal in insomnia based solely on HRV data. Perhaps more importantly, the use of low-to-high frequency ratios of HRV as a surrogate for sympathetic activity remains highly controversial within the field of autonomic neuroscience [32]. Accordingly, there remains a critical scientific gap regarding chronic insomnia and sympathetic hyperarousal.

In the present study, we utilized the gold-standard approach of microneurography to directly record peripheral sympathetic nerve activity. We did not detect a significant difference in resting levels of MSNA between participants with insomnia and controls; in fact, levels of baseline MSNA were remarkably similar. However, when we "stressed" the system using the cold pressor test, participants with insomnia demonstrated significantly higher systolic BP and MSNA reactivity when compared with good sleeper controls. In fact, the order of magnitude of total MSNA hyperarousal was nearly twofold higher in participants with chronic insomnia.

It is important to note that MSNA hyperarousal was observed only when total MSNA was examined; increases of MSNA burst frequency and burst incidence were not different between groups. This may be physiologically relevant given the different insights these various analyses of MSNA provide. As outlined in a recent guidelines paper [15], total MSNA can only be meaningfully compared across groups and different laboratory sessions when the baseline data have been carefully normalized, and when the data have been analyzed as a change during a validated and reproducible stressor [15, 18]. We recently validated the reproducibility of total MSNA, burst frequency, and burst incidence during cold pressor test [18]. Additionally, Kienbaum et al. [33] advanced the concept that there are likely two central sites that contribute to MSNA control in humans—one responsible for whether a burst is generated (i.e. burst occurrence) and one that determines the number of fibers activated (i.e. burst strength). Therefore, our total MSNA data suggest that participants with chronic insomnia have a distinct strategy of sympathetic neural recruitment during stress. Specifically, it appears that for a given change in MSNA burst frequency/incidence during the CPT, participants with insomnia recruit a greater number of sympathetic fibers, at least within an efferent peroneal nerve fascicle.

We acknowledge the following limitations. First, this is a small study, but based on robust gold standard techniques never previously used to study the pathophysiology of insomnia. Second, the strongest associations between insomnia and hypertension have been reported in patients who had objective short sleep duration based on a single night of in-laboratory PSG [6]. Our participants with insomnia did not have shorter sleep than controls on the PSG, but their habitual sleep duration based on 2 weeks of actigraphy was shorter than controls and their WASO was much longer. Third, we obtained our recordings during the morning; it is possible that sympathetic hyperarousal in insomnia may be higher in the evening and/or night, as suggested by observations of elevated nocturnal plasma norepinephrine levels [34]. Finally, although the sex ratio was not significantly different between groups, we acknowledge that the p-value was marginal ($p = 0.13$), with what tended to be a higher number of women in the chronic insomnia group compared with the control group. However, when we repeated the analyses using only data from female participants in each group, the findings were similar. We also acknowledge the lack of data on fat distribution and fitness levels of the participants as a limitation.

In conclusion, participants with chronic insomnia demonstrated markedly blunted sympathetic baroreflex function and augmented MSNA and BP responsiveness to a well-validated stressor. Our findings point at sympathetic overactivity and baroreflex dysfunction as potential mechanisms underlying the reported links between chronic insomnia and hypertension. Taken together with the epidemiological evidence, these observations support the view that chronic insomnia is a psychophysiological disorder associated with an elevated cardiovascular risk. Future longitudinal studies might consider the impact of interventions such as CBT-I and/or pharmacological treatment on sympathetic neural and cardiovascular regulation in patients with chronic insomnia.

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Notes

Conflict of interest statement. The main study sponsor (Merck) has a FDA-approved drug for insomnia (Suvorexant) on the market in the USA and elsewhere; the present study was not a drug trial.

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