Total sleep deprivation alters cardiovascular reactivity to acute stressors in humans

Huan Yang,¹ John J. Durocher,¹ Robert A. Larson,¹ Joseph P. DellaValla,² and Jason R. Carter¹

¹Department of Kinesiology and Integrative Physiology, Michigan Technological University, Houghton, Michigan; and ²Center for Sleep Medicine, Androscoggin Valley Hospital, Berlin, New Hampshire

Submitted 3 May 2012; accepted in final form 16 July 2012

YANG H, DUROCHER JJ, LARSON RA, DELLAVALLA JP, CARTER JR. Total sleep deprivation alters cardiovascular reactivity to acute stressors in humans. J Appl Physiol 113: 903–908, 2012. First published July 19, 2012; doi:10.1152/japplphysiol.00561.2012.—Exaggerated cardiovascular reactivity to mental stress (MS) and cold pressor test (CPT) has been linked to increased risk of cardiovascular disease. Recent epidemiological studies identify sleep deprivation as an important risk factor for hypertension, yet the relations between sleep deprivation and cardiovascular reactivity remain equivocal. We hypothesized that 24-h total sleep deprivation (TSD) would augment cardiovascular reactivity to MS and CPT and blunt the MS-induced forearm vasodilation. Because the associations between TSD and hypertension appear to be stronger in women, a secondary aim was to probe for sex differences. Mean arterial pressure (MAP), heart rate (HR), and muscle sympathetic nerve activity (MSNA) were recorded during MS and CPT in 28 young, healthy subjects (14 men and 14 women) after normal sleep (NS) and 24-h TSD (randomized, crossover design). Forearm vascular conductance (FVC) was recorded during MS. MAP, FVC, and MSNA (n = 10) responses to MS were not different between NS and TSD (condition × time, P > 0.05). Likewise, MAP and MSNA (n = 6) responses to CPT were not different between NS and TSD (condition × time, P > 0.05). In contrast, increases in HR during both MS and CPT were augmented after TSD (condition × time, P ≤ 0.05), and these augmented HR responses persisted during both recoveries. When analyzed for sex differences, cardiovascular reactivity to MS and CPT was not different between sexes (condition × time × sex, P > 0.05). We conclude that TSD does not significantly alter MAP, MSNA, or forearm vascular responses to MS and CPT. The augmented tachycardia responses during and after both acute stressors provide new insight regarding the emerging links among sleep deprivation, stress, and cardiovascular risk.

†Autonomic activity; blood pressure; cold pressor test; mental stress; tachycardia

THE EXTENT OF CARDIOVASCULAR reactivity to mental stress (MS) and cold pressor test (CPT) in young men and women has been shown to have some predictive value regarding the risk of developing cardiovascular disease. Specifically, exaggerated blood pressure reactivity to acute MS or CPT has been repeatedly linked to an increased incidence of hypertension (25, 28, 29, 47, 52). Additionally, studies report that prehypertensive individuals demonstrate an augmented pressor response to acute MS (22, 27, 36, 40), and studies have reported that the magnitude of MS cardiovascular reactivity is associated with resting blood pressure levels years later (28, 29).

In addition to blood pressure reactivity, forearm vascular responses to MS may be an important predictor of cardiovascular risk. Previous work has demonstrated an augmented blood pressure response to acute MS in prehypertensive adults (27, 36, 40), and it has been suggested that this augmentation is due, in part, to a blunted forearm vasodilatory response (36, 40). Similarly, Cardillo et al. (8) have reported that increases in forearm blood flow (FBF) during MS are attenuated in hypertensive adults. Thus evidence is accumulating to suggest that both exaggerated pressor responses and/or blunted forearm vasodilatory responses to acute stress may be important risk factors for hypertension.

Recent epidemiological studies estimate that more than one-third of adults in the United States obtain inadequate sleep (12a, 19). Moreover, studies report an association between inadequate sleep and hypertension (7, 18, 19). The influence of sleep deprivation on cardiovascular reactivity to MS and CPT remains controversial (17, 24). Kato et al. (24) reported that total sleep deprivation (TSD) did not alter cardiovascular reactivity to MS or CPT, whereas a more recent study by Franzen et al. (17) documents an augmented blood pressure reactivity to MS after TSD. Thus it remains unclear if TSD alters cardiovascular reactivity to MS or CPT; moreover, neither study (17, 24) examined the influence of TSD on forearm vascular reactivity to MS. Studies report that sleep deprivation can elicit vascular dysfunction in young, healthy subjects (2, 37, 45). Therefore, the primary purpose of the present study was to examine the influence of 24-h TSD on cardiovascular reactivity to acute MS and CPT. We hypothesized that TSD would augment cardiovascular reactivity to MS and CPT and blunt the forearm vasodilatory response to MS. Additionally, a recent epidemiological study reported that short sleep duration and hypertension are significantly correlated in women but not men (7). Therefore, a secondary purpose of this study was to probe for potential sex differences.

METHODS

Subjects. This study examined 28 healthy adults—14 men (age 22 ± 1 yr, height 176 ± 2 cm, weight 79 ± 4 kg, body mass index 25 ± 1 kg/m²) and 14 women (22 ± 1 yr, height 165 ± 2 cm, weight 63 ± 4 kg, body mass index 23 ± 1 kg/m²). Resting baseline data for these participants have been reported previously (9). Exclusion criteria included history of autonomic dysfunction, cardiovascular disease, and diabetes; all were nonsmokers. All participants demonstrated an apnea-hypopnea index <10 events/h, according to an at-home ApneaLink evaluation (ResMed, San Diego, CA) interpreted by a board-certified sleep physician (J. P. DellaValla). All subjects abstained from exercise, alcohol, and caffeine for at least 12 h prior to laboratory testing. All female subjects had regular menstrual cycles (range 26–30 days) and were tested during the early follicular phase (i.e., days 2–5) of their cycle. Female participants were not taking oral contraceptives or other hormonal supplantations. All subjects received an orientation session, and each

Address for reprint requests and other correspondence: J. R. Carter, Dept. of Kinesiology and Integrative Physiology, Michigan Technological Univ., 1400 Townsend Dr., Houghton, MI 49931 (e-mail: jcarter@mtu.edu).

http://www.jappl.org

8750-7587/12 Copyright © 2012 the American Physiological Society
participant provided his or her written, informed consent. The experimental protocol and procedures were approved by the Michigan Technological University Institutional Review Board.

**Experimental design.** Participants were tested ~1 mo apart to ensure that all females were in the early follicular phase on both testing days. Participants reported to the laboratory for testing at 7:30 AM in the morning after either normal sleep (NS) or 24-h TSD. The order of the trials (i.e., TSD vs. NS) was randomized. Details of the TSD protocol are described previously (9). Wrist actigraphy (Actiwatch-64; Mini Mitter, Philips Respironics, Bend, OR) was used to obtain the average sleep times for at least three consecutive nights preceding each trial. In <10% of nights, actigraphy data were not available; thus self-reported sleep diary data were used. A board-certified sleep physician (J. P. DellaValla) analyzed all actigraphy and sleep diary data. Participants were getting adequate sleep before the TSD protocol are described previously (9). Wrist actigraphy (Actiwatch-64; Mini Mitter, Philips Respironics, Bend, OR) was used to obtain the average sleep times for at least three consecutive nights preceding each trial. In <10% of nights, actigraphy data were not available; thus self-reported sleep diary data were used. A board-certified sleep physician (J. P. DellaValla) analyzed all actigraphy and sleep diary data. Participants were getting adequate sleep before the TSD protocol are described previously (9). Wrist actigraphy (Actiwatch-64; Mini Mitter, Philips Respironics, Bend, OR) was used to obtain the average sleep times for at least three consecutive nights preceding each trial. In <10% of nights, actigraphy data were not available; thus self-reported sleep diary data were used. A board-certified sleep physician (J. P. DellaValla) analyzed all actigraphy and sleep diary data. Participants were getting adequate sleep before the TSD protocol are described previously (9).

On each testing day (NS and TSD), three resting-seated blood pressures were taken at 7:30 AM after at least 5 min of quiet rest. Following the blood pressure recordings, state anxiety was measured using the State-Trait Anxiety Inventory questionnaire for adults (41), followed by fasting venipuncture to determine levels of estradiol, progesterone, and testosterone. Following these initial measurements, participants were situated in the supine position on a laboratory table for cardiovascular and neural instrumentation. Following a 10-min baseline reported previously (9), there was a 10-min nonrecorded period in which the forearm venous occlusion plethysmography (VOP) was instrumented. Following the VOP instrumentation, all subjects participated in a MS trial that consisted of a 5-min supine baseline, 5 min of MS (arithmetic), and 5 min of recovery. The mental arithmetic involved subtracting a single digit number (e.g., six or seven) continuously from random two- to three-digit numbers while investigators verbally pressured the subject to subtract faster. Immediately following the MS protocol, subjects reported their perceived stress during the mental arithmetic using a standard scale of zero to four (6). Following a 10-min nonrecorded recovery, which allowed for removal of the VOP equipment, subjects performed a CPT trial, which consisted of a 3-min baseline, 2 min of CPT (hand submerged in ice water, ~1°C), and a 3-min recovery.

**Measurements.** Beat-to-beat arterial blood pressure was recorded continuously using a Finometer (Finapres Medical Systems, Amsterdam, The Netherlands). Three consecutive supine blood pressures were taken prior to both the MS and CPT baselines via an automated sphygmomanometer (Omron HEM-907XL, Omron Healthcare, Kyoto, Japan) to calibrate the Finometer. Arterial blood pressures were expressed as systolic (SAP), diastolic, and mean (MAP) arterial blood pressures. Heart rate (HR) was recorded continuously via a three-lead electrocardiogram, and respiratory rate was measured continuously with the use of a pneumobelt. Multifiber recordings of muscle sympathetic nerve activity (MSNA) were obtained by inserting a tungsten microelectrode (FHC, Bowdoin, ME) into the peroneal nerve of the right leg, while a tin electrode placed on the right wrist was used as a ground. The occluding cuff placed on the wrist was inflated to 220 mmHg, whereas the upper-arm cuff was inflated to 60 mmHg for 8 s and deflated for 7 s (i.e., 15-s blood flow intervals). Forearm vascular conductance (FVC) was calculated as FBF divided by MAP.

**Data analysis.** Data 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 (bursts/min), burst incidence (bursts/100 heartbeats), and total MSNA (i.e., the sum of the normalized burst areas/min). Due to the complexity of the experimental approach (see Discussion for more detail), successful and complete recordings of MSNA throughout the MS and CPT trials were limited to n = 10 and n = 6, respectively.

**Statistical analysis.** All data were analyzed statistically using commercial software (SPSS 20.0, IBM SPSS, Armonk, NY). We used repeated-measures ANOVA with time (baseline, intervention, and recovery) and condition (NS vs. TSD) as within-subjects factors and sex (men vs. women) as a between-subjects factor. Post hoc analysis was performed when significant condition × time interactions were detected. Pearson correlations were used to examine the relations between changes of HR and percent changes of FVC during MS. Results are expressed as mean ± SE. Means were considered significantly different at P < 0.05.

## RESULTS

**Baseline hemodynamics.** Our previous study reported that TSD elicited increases of resting-seated and supine baseline blood pressure (9). Consistent with this, the present study reveals that TSD increased baseline SAP immediately preceding the MS and CPT trials (P < 0.05). TSD did not alter resting HR, FBF, and FVC during the baselines preceding MS or CPT (condition × sex, P > 0.05).

**Cardiovascular and neural reactivity to MS and CPT.** Figure 1 depicts that MS and CPT elicited robust increases in both MAP and HR (time, P < 0.01). Whereas the increases in MAP during MS and CPT were similar between NS and TSD (condition × time, P = 0.35 and P = 0.31, respectively), TSD elicited an augmented HR reactivity (MS: condition × time, P = 0.05; CPT: P < 0.01). Likewise, HR responses remained elevated during both stress recovery periods following TSD compared with NS (condition × time, P < 0.01). MSNA reactivity to MS [change in (Δ2 ± 1 vs. Δ0 ± 1 bursts/min; condition × time, P = 0.40; n = 10] and CPT (Δ14 ± 4 vs. Δ14 ± 6 bursts/min; condition × time, P = 0.48; n = 6) was similar between NS and TSD. MSNA reactivity to MS and CPT was also similar between NS and TSD when expressed as burst incidence and total MSNA (data not reported).

Figure 2 demonstrates that FBF and FVC increased significantly during 5-min MS (time, P < 0.01), and these responses were not different between NS and TSD. Specifically, TSD did not alter ΔFBF (Δ67 ± 12 vs. Δ83 ± 13%; condition × time, P = 0.30) or ΔFVC (Δ47 ± 8 vs. Δ59 ± 11%; condition × time, P = 0.25). Changes in HR were significantly correlated to changes in FVC during MS after NS (r = 0.59, P < 0.01) and TSD (r = 0.61, P < 0.01). Importantly, perceived stress was not different during the two trials (2.3 ± 0.2 vs. 2.5 ± 0.1 arbitrary units, P = 0.316).

**Sex comparisons.** There were no sex differences in the MAP or HR reactivities to MS (condition × time × sex, P > 0.05) or CPT (condition × time × sex, P > 0.05) following either sleep condition. Similarly, changes in FBF (condition ×
DISCUSSION

The current study investigated the influence of 24-h TSD on cardiovascular reactivity to MS and CPT. We report three new findings. First, TSD did not alter the MAP reactivity to MS or CPT; however, TSD elicited an augmented HR reactivity during both MS and CPT. Moreover, this elevated HR response during TSD persisted throughout the recovery periods of both stressors. Second, contrary to our original hypothesis, increases in FBF and FVC during MS were not blunted by TSD. Third, no sex differences were observed among the MAP, HR, or forearm vascular reactivity after TSD. Our findings suggest that sleep deprivation elicits heightened HR reactivity and delayed HR recovery to MS and CPT; these findings may help to explain the emerging links among sleep deprivation, stress, and cardiovascular disease.

Large-scale longitudinal studies have documented that augmented cardiovascular reactivity to acute stressors such as MS and CPT is linked to an increased risk of developing hypertension (13, 26, 28, 43, 46, 52). Moreover, smaller observation studies report that both prehypertensive adults (22, 27, 36, 40) and subjects with a family history of hypertension (30, 51) demonstrated augmented blood pressure responses to MS. Thus evidence is accumulating to suggest that exaggerated cardiovascular reactivity to stress is linked to an increased incidence of future hypertension.

Recent epidemiological studies demonstrate a consistent link between sleep deprivation and hypertension in humans (7, 18, 19). However, the influence of TSD on cardiovascular reactivity to acute stressors remains controversial (17, 24). Kato et al. (24) reported that cardiovascular reactivity to acute stress was not different between NS and TSD. However, it is important to note that the MS protocol used in the study (24) failed to elicit significant increases in HR or blood pressure during MS in the control (i.e., NS) condition, thus limiting interpretation. Our laboratory (10–12) and others (3, 6, 20, 33, 49) consistently report robust increases in both HR and blood pressure during MS. In contrast to the findings of Kato et al.
elicited increases of FBF and FVC. TSD did not alter these responses. *P < 0.05 vs. baseline. N.S., not significant.

correlations are stronger at rest compared with sympathoexcit-
spillover are correlated, Wallin et al. (48) report that these
speculation. First, whereas MSNA and cardiac norepinephrine
there are several reasons why we are not comfortable with this
primary contributor to the HR reactivity after TSD. However,
heightened cardiac sympathetic activation is unlikely to be a
jects. Because MSNA responses to MS and CPT were similar
for TSD after NS and 24 h of TSD. MS significantly
evolved increases of FBF and FVC. TSD did not alter these responses. *P <
0.05 vs. baseline. N.S., not significant.

(24), a more recent study by Franzen et al. (17) reported an
augmented SAP response to MS after TSD. Thus the influence
of TSD on cardiovascular reactivity remains unresolved.

In the present study, we report that HR reactivity to both MS
and CPT was exaggerated significantly after TSD, whereas
blood pressure reactivities to both stressors were similar be-
tween NS and TSD. Light et al. (26) reported that individuals
with high HR reactivity to acute stress were more likely to
develop hypertension and tachycardia at a 10- to 15-yr fol-
low-up compared with low HR reactors. Similarly, Stewart
and France (43) demonstrated an association between heightened
HR reactivity to MS and elevated SAP in a 3-yr follow-up inves-
tigation. Thus the augmented HR reactivities to MS and
CPT after TSD may have important clinical relevance.

Wallin et al. (48) have shown a positive correlation between
MSNA and cardiac norepinephrine spillover in healthy sub-
jects. Because MSNA responses to MS and CPT were similar
between NS and TSD, it is tempting to speculate that the
heightened cardiac sympathetic activation is unlikely to be a
primary contributor to the HR reactivity after TSD. However,
there are several reasons why we are not comfortable with this
speculation. First, whereas MSNA and cardiac norepinephrine
spillover are correlated, Wallin et al. (48) report that these
correlations are stronger at rest compared with sympathoexcit-
atory maneuvers. Moreover, the authors suggest that the bal-
ance between sympathetic outflows to heart and skeletal mus-
cle differs between maneuvers (i.e., handgrip exercise vs. MS).
Second, recent studies suggest differentiation of sympathetic
outflow to the heart and skeletal muscle in certain cardiovas-
cular disease states (15, 32). Likewise, Rundqvist et al. (35)
demonstrated that early, mild heart failure is associated with
augmented cardiac sympathetic activity but not sympathetic
outflow to the skeletal muscle vasculature. Although our sub-
jects were young and healthy, the TSD trial did elicit an acute
hypertensive response. Collectively, it would appear that an
investigation examining the effects of sleep deprivation on
cardiac norepinephrine spillover might be warranted to better
understand the heightened HR reactivity reported in the present
study. Increases in cardiac sympathetic outflow are important
to human hypertension (14, 16).

For decades, cardiovascular reactivity has been examined in
the laboratory with few attempts to generalize reactivity as-
sessed in the laboratory to the “real world” (39). This remains
a limitation of the cardiovascular reactivity theory. However, it
appears that the use of data “aggregation” across multiple
stressors can improve generalizability (39). Additionally, evi-
dence is accumulating to suggest that cardiovascular recovery
from stress may be useful in predicting long-term cardiovas-
cular health (21, 26, 38, 42–44). Specifically, Heponieni et al.
(21) reported that faster HR recovery after the MS was related
to lower levels of carotid atherosclerosis. Additionally, Stewart
et al. (44) demonstrated that faster HR recovery from five
psychological tasks was related to a lower risk of developing
hypertension at a 3-yr follow-up. In the present study, we
found that TSD elicited a delayed HR recovery response after
both MS and CPT. When combined with the augmented HR
reactivity during both acute stressors, these findings may pro-
vide valuable insight into the emerging links among sleep
depression, stress, and cardiovascular disease. The aggrega-
tion across stressors (i.e., MS and CPT) and trial time (i.e.,
actual stressor and recovery) lends credibility to the idea that
TSD elicits heightened HR reactivity to acute stress.

MS elicits a consistent and reproducible forearm vasodila-
tory response (4, 5, 10). There is growing evidence to suggest
that blunted forearm vasodilation is a potential mechanism for
the augmented pressor response to MS in at-risk populations
(8, 34, 36). Weil et al. (50) reported recently that inadequate
sleep elicits an excess forearm vasoconstrictor tone, which
the authors suggest contributes to an increased risk of
hypertension and other forms of cardiovascular disease.
Additionally, studies have demonstrated vascular dysfunc-
tion in both large-conductance artery (i.e., brachial artery)
(2, 45) and cutaneous microvascular beds (37) after chronic
and/or acute sleep deprivation. FVC measurements via VOP
adequately reflect vasodilation and/or vasoconstriction in
the limb vasculature (31). Contrary to our initial hypothesis,
our FVC data indicate that MS elicits similar forearm
vasodilatory responses after NS and TSD. In fact, our data
demonstrate a trend toward heightened forearm vasodilation
after TSD. Pike et al. (33) reported a striking correlation
between HR and FVC responses to MS and suggested that
mechanical stimulation associated with higher HR reactivity
is a key contributor to increases of FVC during MS. We
observed similar correlations between FVC and HR as that
reported by Pike et al. (33), and these relations between

![Fig. 2. Changes in forearm blood flow (ΔFBF) and forearm vascular conduc-
tance (ΔFVC) to MS (n = 25) after NS and 24 h of TSD. MS significantly
evolved increases of FBF and FVC. TSD did not alter these responses. *P <
0.05 vs. baseline. N.S., not significant.]
FVC and HR were present after both NS and TSD. That said, TSD did not statistically alter FVC responses to MS. This finding is consistent with the idea that changes in forearm vascular tone are not induced by 24-h TSD but instead require “habitual short sleep duration” (50).

A recent epidemiological study reports that the associations between short sleep duration and the risk of hypertension are stronger in women compared with men (7). Therefore, a secondary aim of this study was to probe for sex differences in cardiovascular reactivity after TSD. Our data indicate that there are no sex differences in blood pressure or HR reactivities to MS and CPT following TSD. Furthermore, there were no sex differences in the FVC response to MS. Thus the stronger associations between short sleep duration and the risk of hypertension do not appear to be related to different cardiovascular reactivity to acute stressors in men and women.

We recognize three important study limitations. First, our experimental approach used a 24-h TSD protocol. Whereas this remains a primary experimental intervention for examining physiological responses to inadequate sleep, it is recognized that accumulated sleep debt via multiple days of short sleep duration is much more common in a nonlaboratory setting (i.e., daily living). Thus we caution the translation of our findings beyond the context of 24-h TSD. Given the augmented HR reactivity to both MS and CPT reported in the present study, we believe that future work using the more complex and time-intensive sleep-restriction model (i.e., sleep time <6 h/night over consecutive days) appears warranted. Second, our recent study examining resting baseline responsiveness to TSD with the present cohort of subjects reported MSNA in 10 men and 10 women (9). Unfortunately, the microneurography electrode was dislodged during several of the MS and/or CPT trials in our subjects, thus limiting our MSNA sample sizes. Given the randomized, crossover approach (i.e., NS vs. TSD), we were not comfortable “repositioning” the electrode and rerunning baselines and interventions; we believed that providing a similar laboratory environment and experimental sequence was essential for the cardiovascular reactivity comparisons. Whereas the MSNA data were critical for our resting baseline study (9), it was not viewed as essential for the MS and CPT trials, because our primary hypotheses focused on the cardiovascular reactivity. In the present study, we were able to statistically analyze the MSNA data with regard to our primary hypothesis (i.e., TSD vs. NS) but were unable to probe our secondary hypothesis (i.e., sex difference). Third, TSD has been shown to influence the renal system (i.e., excess natriuresis and osmotic diuresis), which could affect hemodynamic changes (23). We did not monitor hydration status or renal hormone levels. Future work in this area might include measurements of renal hormones, catecholamines, and hydration status.

In summary, 24-h TSD does not affect the blood pressure reactivity to MS or CPT nor does it influence FVC reactivity to MS. In contrast, TSD elicits an augmented HR reactivity and delayed recovery during both MS and CPT. This exaggerated HR reactivity after TSD is of clinical relevance (21, 26, 43, 44) and provides new and valuable insight regarding the complex and poorly understood relations among sleep deprivation, stress, and cardiovascular disease.

ACKNOWLEDGMENTS

The authors thank Thomas Drummer, Christopher Schwartz, Michelle King, and Kristen Reed for their technical assistance. We also thank all of our subjects for their participation.

GRANTS

Support for this project was provided by the National Heart, Lung, and Blood Institute (HL-098676).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


REFERENCES
