行政院國家科學委員會專題研究計畫　成果報告

睡眠限制如何影響休息時健康年輕人的交感神經活性、代謝與血流動力變化----- 結果可能隨受試姿勢和時間而改變

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Paradoxical cardiovascular responses facing elevated metabolic rate after sleep restriction in subjects sitting upright

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Running head: BP, HR, breathing and $\dot{V}O_2$ after sleep restriction

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ABSTRACT
To clarify whether sleep restriction (SR) affects hemodynamics and breathing patterns via a sympathetic tone potentiality, we conducted a dose response experiment before and after SR. We assessed cardiopulmonary parameters at a resting, sitting upright position in eleven healthy young subjects after a normal sleep and after one- and two-days of SRs. In comparison with one night of normal sleep, the nocturnal SR resulted in a decreased heart rate (83±14 vs 77±9, and vs 78±12 beats/min; after normal sleep vs after one-day SR, and vs after two-day SR, both $p < 0.05$), reductions in diastolic (68±9 vs 61±4, and vs 60±8 mm Hg, both $p < 0.05$) and mean BPs (83±10 vs 76±6, and vs 76±9 mm Hg, both $p < 0.01$) as well as a rise in oxygen pulse (3.4±1.6 vs 4.2±1.3, and vs 4.2±1.5 mL/beat, $p < 0.005$ and < 0.05, respectively) coupled with declinations of ventilation equivalents for oxygen uptake (44.8±12.7 vs 36.7±7.8, and vs 36.5±6.8, both $p < 0.01$) and carbon dioxide output (45.4±9.0 vs 41.3±6.1, and vs 40.9±5.5, $p = 0.07$ and < 0.05, respectively), while facing an elevated basal metabolic rate (268±74 vs 312±65, and vs 309±71 mL/min, both $p < 0.05$). In contrast, minute ventilation, breath frequency and tidal volume were not affected by SR.

However, there were no differences between the one- and two-day SR values in all above parameters. SR may speculatively lower sympathetic-activity-related hemodynamics, but SR does not appear to elicit breath pattern changes with an increased metabolic demand.

KEYWORDS heart rate, blood pressure, sleep deprivation, gas exchange, metabolic rate

摘要

我們進行這項研究的目的是要進一步瞭解是否睡眠制約，經由代謝率的變動，交感神經活性的升降，進而影響血流動力變化。於是設計在劑量差別的睡眠制約，即連續兩天，而每天僅能入睡三小時的安排下，量測之前之後的血流動力學變化。11 位健康年輕人（5 名女性）在正常睡眠(D0)或連續兩晚睡眠制約後(D1 & D2)，於次日早晨，於靜坐狀態下，接受非侵襲性氣體分析：例如通氣量（$\dot{V}E$）、攝氧量($\dot{V}O2$)、二氧化碳排除量（$\dot{V}CO2$）、攝氧通氣當量 ($\dot{V}E/\dot{V}O2$) 、二氧化碳通氣當量($\dot{V}E/\dot{V}CO2$)與氧脈（O2 Pluse）；同時量測血壓（Blood Pressure）並藉由心電圖（Electrocardiography）計算心率變化。結果發現：相較於正常睡眠後，一天或兩天睡眠制約，明顯導致代謝率上升；而心率、舒張壓及平均血壓明顯下降，合併氧脈上升；而重力相

關的肺部氣體交換結構－通氣當量（$\dot{V}E/\dot{V}O2$ 及 $\dot{V}E/\dot{V}CO2$）亦明顯下降（與 D0 相較 D1 和 D2 有意義差別數據分別如下：攝氧量= 268±74 相較 312±65 和 309±71 mL/min，心率= 83±14 相較 77±9 和 78±12 beats/min，舒張壓= 68±9 相較 61±4 和 60±8 mmHg，平均血壓=83±10 相較 76±6 和 76±9 mmHg，氧脈＝3.4± 1.6 相較 4.2±1.3 和 4.2±1.5 mL/beat，攝氧通氣當量= 44.8±12.7 相較 36.7±7.8 和 36.5±6.8，二氧化碳通氣當量= 45.5± 9.0 相較 41.3±6.1 和 40.9±5.5）。上述數值並未因一天或兩天睡眠制約而有所差別。因此面對因睡眠制約而上昇的代謝率，卻結合反向心率及血壓的抑制。這種動力學的特異變化極有可能危害心血管系統。

關鍵字：心率、血壓、睡眠剝奪、氣體交換、代謝率

INTRODUCTION

High cardiovascular morbidity related to sleep loss has been frequently reported (Steenland et al., 1996), but the definite cause has not yet been elucidated. Spiegel et al. (1999) reported that nocturnal sleep restriction (SR) to as little as four hours caused augmentation of sympathetic nervous activities and increased evening cortisol levels.In contrast, diminished sympathetic nerve activities, coupled with a constant heart rate (HR) but increased blood pressure (BP) after sleep deprivation, have also been reported in recent experiments (Kato et al., 2000; Ogawa, et al., 2003), with sympathetic muscle nerve activity recorded in the supine position. A consensus on whether increased or decreased sympathetic activity affects the hemodynamics after SR, has not yet been reached. Even so, the fact that sleep loss potentially affects hemodynamics via the autonomic nervous system is well accepted (Spiegel et al., 1999; Mancia et al., 1993; Somers et al., 1993).

Most studies have investigated the impact of sleep loss on hemodynamic responses and autonomic functions in the recumbent position. However, Cooke et al. (1999) examined a gravity challenging effect on cardiovascular and autonomic functions and found that HR, BP and sympathetic muscle nerve activity increased proportionally with the tilted angle in healthy volunteers. Likewise, similar findings, such as the elevation of BP and sympathetic nerve activity and a decrease in HR, after application of gravitational stress in animal (Kerman et al., 1998; Gotoh et al., 2004) and human studies (Yates et al., 1999) have been reported. Nonetheless, these studies have conjectured that both the baroreflex and the vestibulosympathetic reflex played major roles in the hemodynamic responses. Besides, in animal studies, vestibular (Yates et al., 1995) and cerebellar processes (Xu et al., 1994 and 1995) were confirmed to affect sympathetic outflow and breathing pattern via alterations in Purkinje cell-fastigial nucleus interaction changes (O'Hearn and Molliver, 1997; Yates et al., 1996), partucilarly when facing hemodynamic stress. Accordingly, if physiological parameters are recorded in the sitting position, not only is the present study simulating a real life gravity effect, but it should also be more sensitive in assessing changes of sympathetic-tone-related hemodynamics and breath patterns after SR.

Moreover, the metabolic change should be an essential issue in testing hemodynamic responses (Wasserman et al., 1999) either in rest or during exercise. Actually, Chen (1991) had demonstrated that after one-night of complete sleep loss, the resting minute oxygen consumption ($\dot{V}O_2$) elevated substantially. Furthermore, in animal (Bergmann et al., 1989) and human studies (Fiorica et al., 1968; Bonnet et al., 1991), after partial

SR or a complete night of sleep deprivation the metabolic rate increased significantly, which was postulated as the consequence of compensatory mechanism(s) for impaired thermoregulation (Bergmann et al., 1989) via increasing thyroid hormones (Palmblad, et al., 1979) and/or growth hormone (Vgntzas et al., 1999).

Therefore, we hypothesized that SR would increase the basal metabolic demand accompanied by decreased-sympathetic-activity-related hemodynamic changes and a consequential alterations of the breathing pattern, particularly when an investigation is performed at a position with a greater gravity challenge. We also hypothesized that the dosage effect of SR would exist. To observe the effects of SR on hemodynamics and respiration and to examine its dosage effect, HR, BP, breathing pattern and gas exchanges in the young healthy subjects were non-invasively measured at a resting, sitting upright position on three consecutive mornings, i.e. after one night of normal sleep and after one- and two-days of SR.

METHOD

Subjects

The young healthy volunteers were recruited after they had abstained from caffeine drinks and exercise for 24 hours. All subjects were non-smokers who had never fainted and had not taken any medicine.

They all had normal daily sleep patterns with a duration of 7-8 hours.

Female subjects, who tested negative for pregnancy, were not studied during or within two days of menses to eliminate potential confounding effects of menses. This study was reviewed and approved by the Institutional Review Board of Chung-Shan Medical University Hospital in Taichung, Taiwan. The approved consent form was signed by each subject prior to participation.

Protocol

Subjects were informed of the sleep schedule for this study. The first night would be a normal sleep at home (around 11:00 pm to 6:00 am) and then the subjects would spend two nights with SR in our sleep center.

At the sleep center, the surrounding temperature was maintained at about 23°C and light intensity was < 300 lux. During the period of SR, the subjects were accompanied by our staff and were instructed to remain inactive, but reading, television watching, music listening, talking, video games and table games were permitted. During the non-sleep time, the staff checked the subjects every 15 minutes to ensure that they were awake. The sleep time was set from 3:30 am to 6:30 am. For most of the subjects, this period just presented as a late bedtime with a relatively

normal awakening time. In the morning, after showers, subjects were given a light breakfast before measurements.

Measurements in Gas Exchange and Hemodynamic Variables

The participants were not allowed to eat two hours before testing. The noninvasive gas exchange, breathing pattern and hemodynamic measurements were performed around 9:00 am after normal sleep or after SR. Each subject was asked to sit silently in a chair for more than fifteen minutes before testing. The parameters of gas exchanges and breathing pattern included minute exhaled ventilatory volume ($\dot{V}E$), tidal volume, breath frequency, $\dot{V}O_2$, and minute carbon dioxide production ($\dot{V}CO_2$).

Additionally, the derived variables, including the respiratory exchange ratio, end tidal O_2 and CO_2 partial pressures, the ventilatory equivalents for $\dot{V}O_2$ ($\dot{V}E/\dot{V}O_2$) and for $\dot{V}CO_2$ ($\dot{V}E/\dot{V}CO_2$) as well as oxygen uptake per min per heart beat (O_2 Pulse) were all calculated off-line. Both $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ are the representatives of ventilation versus perfusion status for pulmonary gas exchange (Wasserman et al., 1967).

Cardiovascular parameters, including BP at the left brachial artery (taken by using autonomic blood pressure cuff every minute; Tango, Sun Tech Medical Instruments Inc, Raleigh, NC USA), oxygen saturation of finger (In vivo 4500 plus, Invivo Research Inc. USA), and a 12-lead electrocardiogram (Marquette CardioSys v 3.01) were recorded simultaneously. All signals were relayed to a digital recording system (Vmax229d Cardiopulmonary Exercise Testing Instrument; SensorMedics, Yorba Linda, CA), which calculated a breath-by-breath time course of gas exchanges, BP, HR and oxygen saturation. All the data were converted to points at one-second intervals by interpolation.

DATA ANALYSIS

The last 3-min of data from a 10-min measurement of gas exchanges and hemodynamics, described as above, were averaged for statistical analysis. All data presented in the text, tables, and figures are means ± standard deviation.

Differences in gas-exchanges, breathing and hemodynamic variables and derivatives after normal sleep, and after one- and two-days of SR were determined with a 2-tailed paired Student's *t* test. Statistical significance was defined as $p < 0.05$.

RESULTS

All eleven subjects (19±1, 20±2 years of age; 159±4, 173±6 cm in height; and 50±7, 69±6 kg in body weight in 5 females and 6 males,

respectively) completed the consecutive three day course.

Of the hemodynamic variables, HR (83±14 vs 77±9, and vs 78±12 beats/min; after normal sleep vs after one-day SR, and vs two-day SR, both $p < 0.05$), diastolic BP (68±9 vs 61±4, and vs 60±8 mm Hg, both $p < 0.005$) and mean BP (83±10 vs 76±6, and vs 76±9 mm Hg, both $p<0.01$) were significantly lower after either one- or two-days of SR. However, systolic BP was not affected by either one- or two-days of SR (Fig. 1).

For gas exchange measurements, $\dot{V}O_2$ (268±74 vs 312±65, and vs 309±71 mL/min, after normal sleep vs after one-day SR, and vs two-day SR, both $p < 0.05$) and O_2 Pulse (3.4±1.6 vs 4.2±1.3, and vs 4.2±1.5 mL/beat, $p < 0.005$ and < 0.05, respectively) increased significantly after SR when compared to the values after normal sleep. The finger's O_2 saturation, breathing and derived gas exchange parameters including $\dot{V}CO_2$, respiratory exchange ratio, $\dot{V}E$, tidal volume, breath frequency, end tidal O_2 and CO_2 partial pressures were not affected by SR (Table and Fig. 2).

The $\dot{V}E/\dot{V}O_2$ declined significantly after SR. The $\dot{V}E/\dot{V}CO_2$ also decreased substantially ($p = 0.07$) post one-day of SR and significantly ($p < 0.05$) after one-day and two-days of SR, respectively in comparison with the after normal sleep values (Table and Fig. 3).

There was no statistical significance between the one- and two-day SR values for all the above hemodynamic, breathing pattern and gas exchange parameters. No dosage effect was found.

DISCUSSION

In the present study, we evaluated the impact of SR on hemodynamics, breathing and gas exchanges at a resting, sitting position in healthy subjects. After SR, an increased $\dot{V}O_2$, and O_2 pulse; a reduced HR, mean and diastolic BPs; and declined ventilatory equivalents for $\dot{V}CO_2$ and $\dot{V}O_2$ paired with constant minute ventilation, breath frequency and tidal volume were found.

An increased O_2 pulse can be explained as an increased stroke volume because the arterio-venous O_2 content difference is relatively constant when tested at rest (Koike, et al., 1990). The reductions of $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ just suggest that a reduced alveolar dead space develops (Wasserman, 1978) and is associated with the improved efficiency in pulmonary gas exchange post SR. This implies that an increased pulmonary blood flow, secondary to the increased metabolic rate (probably like during exercise for example Wasserman, 1978), replenishes previous nonperfused or underperfused alveoli (particularly in

upper lung portion when sitting upright), and minimizes the heterogeneity of ventilation-perfusion matching.Thus, it is illogically to interpret SR as good for pulmonary gas exchanges. On the contrary, when meeting an elevated basal metabolic demand, the respiratory and hemodynamic responses after SR manifest uniquely, that is, without eliciting breathing pattern changes, they negate the cardiac chronotropic effect paired with an increasing stroke volume and a reduction in the total peripheral resistance.

In determining the possible mechanism(s) making BP and HR changes after sleep loss, the investigators always made it a precondition that the metabolic rates were not altered even though this is not without controversy. Chen (1991) previously showed that one night of complete sleep loss resulted in a substantially increased resting $\dot{V}O_2$ ($p = 0.06$). Furthermore, in animal (Everson et al., 1989) and human (Fiorica et al., 1968; Bonnet et al., 1991) studies, the increased metabolic rate caused by sleep loss could be the consequential compensation for impaired thermoregulation (Landis et al., 1998; Everson et al., 1989). The increased thyroid hormone (Palmblad et al., 1979; Balzano et al., 1990) and/or growth hormone (Vgntzas et al., 1999) might account for it, although an agreement has not yet been reached. Therefore, it might be reasonable to take metabolic demand into consideration when investigating hemodynamic changes.

After one night of staying awake in a bed in the supine position, Kato et al. (2000) and Ogawa et al. (2003) found that their subjects had an unchanged HR, increased mean and diastolic BPs, unchanged plasma catecholamine levels, but reduced muscular sympathetic nerve activities the next morning. These findings were attributed either to peripheral mediators (Kato et al., 2000) or (Ogawa et al., 2003) to a less-steep central arterial baroreflex resetting. However, there are several pitfalls that remain unsolved for these two interpretations (Shamsuzzaman et al., 2003). Plus, metabolic rate alteration was not considered in these two studies (Kato et al., 2000; Ogawa et al., 2003) and all measurements were performed before the subjects left their beds. We might ascribe the disparity of BP changes between the previous studies and ours to the following reasons: (1) the peripheral vessel resistance, based on gravity-related sympathetic activity, declined more dominantly after SR in our sitting upright subjects.That SR negates the resistance of vessels most likely outweighs the effect of a presumed increase in blood flow (or cardiac output) from the elevated metabolic rate (Stringer et al., 1997). (2) With little gravity effect in the recumbent position, in their subjects, the increased metabolic rate (actually, not mentioned in their articles) would elevate BP, if the corresponding vasodilatation and/or increased vessel recruitment would not develop enough to completely alleviate the effect

of this presumed increase in blood flow (Stringer et al., 1997). In this case, a speculative elevation in stroke volume, offsetting the lowered peripheral vascular resistance, leads to drops in diastolic and mean BPs but a constant systolic BP, accompanied by a reduction in HR.

After all, there is still no consensus on how sleep loss affects sympathetic activities. Previously, SR was used as a strategy to treat patients with major depression by diminishing their high evening serum cortisol levels. Spiegel et al. (1999) suggested that SR might decrease sympathetic activities in these patients. After staying awake for 30 hours (Holmes et al., 2002), healthy subjects had a reduction in HR in the recumbent position, which was postulated as declined cardiac sympathetic activity associated with constant parasympathetic activity. Furthermore, from a neuroendocrinological viewpoint, Vgntzas et al. (1999) reported that cortisol secretion reduced significantly concomitant with the first-four-hour growth hormone elevation after one night's sleep loss in healthy subjects, but not in patients with sleep disordered breathing. It appears that different groups of recruited subjects, variant timing for data collection and distinct protocol for SR might be the essential determinants for the diverse results.

In a tilting table study, Cooke et al. (1999) found that HR, BP and sympathetic muscle nerve activity increased proportionally with the tilt angle, indicating that muscular sympathetic nerve activity is definitely gravity dependent. Furthermore, Gotoh et al. (2004) in their animal research of gravity stress effect, reported that there was a striking increase in renal sympathetic activities, a remarkable surging of arterial BP and a decrease in HR in sinoaortic denervated rats (baroreflex damaged) versus rats with a sole vestibular lesion (vestibulosympathetic reflex impaired) or with both a vestibular lesion and sinoaortic denervation. Consequently, it was postulated that the arterial BP control system relevant to gravitation stress, was the combination of vestibular feedforward and baroreflex feedback systems. Similar hemodynamic changes were found in a human research after gravitational stress application (Yates et al., 1999). This gravitation stress effect, however, was considerably attenuated in vestibular dysfunction patients. Moreover, from studies in normal subjects and in children with congenital central hypoventilation syndrome, as well as in animals, recent evidence implicates vestibular (Yates et al., 1995) and cerebellar processes, particularly relevant to the cerebellar fastigial nucleus (Harper, 2000), as an "error correction" role, in modulating appropriate breathing control responses to O_2, CO_2 (Xu et al., 1994 and 1995), and BP (Lutherer et al., 1983). In the current study,

there were no signs of respiratory compensation triggered (the end tidal O_2 and CO_2 partial pressure, tidal volume and breathing frequency were all unchanged) after SR, when facing an increase in $\dot{V}O_2$ and decreases in HR and BP (diastolic and mean BPs). This might illustrate that SR eventually attenuates sensitivities in the vestibulosympathetic reflex and the baroreflex without evoking a vestibulo- or cerebello-respiratory response even when meeting a significantly elevated metabolic status.

The hemodynamics and gas exchanges after SR, in the current study, are similar to, but not as severe as in Chen's study (1991) where the subjects were tested after one night of complete sleep loss. In her study, all variables were measured with subjects in a resting, sitting upright position on a bike seat before the initiation of cycling exercise. Chen's subjects developed decreases in HR, plasma catecholamine, and partial pressure of end tidal CO_2 accompanied by a high arterial pH. These findings corresponded with the situation just before vasovagal syncope (Lagi et al. 2001). In previous studies, slow wave sleep dramatically modulated the baroreceptor reflex (Mancia 1993; Somers et al., 1993) and was dominantly reserved even in short term napping after sleep loss (Tilley and Wilkinson, 1984). The findings in these studies might explain why the hemodynamic derangement after one night of complete sleep loss was worse than that after one- or two-days of incomplete SR. Our results show that there is no dosage effect on hemodynamic and gas exchange parameters between one- and two-day SRs. Whether one night of complete sleep loss modulates sympathetic hemodynamics more negatively compared to one-day or two-days of SR, needs further study.

A possible limitation of our study is that we did not measure hemodynamic, breathing pattern and gas exchange parameters at both the supine and sitting positions, which makes it difficult to tell the differences between the two positions. It is unlikely, however, that the metabolic rate has a significant difference in these two postures' assessments.

Moreover, without continuous monitoring of pulse-by-pulse BP invasively or non-invasively, muscular sympathetic nerve activity, and an electrocardiograph we cannot realize the HR-variability-related sympathetic-parasympathetic activities and the sensitivity changes in the vestibulosympathetic reflex and the baroreflex after SR. Admittedly, our study was not designed to confirm or negate any of the possible mechanisms involved in sympathetic activity changes found in previous research (Kant et al., 1984; Kato et al., 2000; Ogawa et al., 2003; Leproult et al., 1997; Spiegel et al., 1999). Instead, it highlights a potential probability that the recruited subject group, research protocol and altered metabolic rate might be essential in figuring out how basal sympathetic activities and hemodynamics changes develop after SR.

In summary, this study shows that one- or two-days of SR leads to a diminished HR, reduced diastolic and mean BPs, and speculatively, an increased stroke volume and cardiac output, which is possibly secondary to a decrease in systemic vascular resistance and an elevated resting metabolic rate. A concomitant improvement in pulmonary ventilatory versus perfusion matching might be partially accounted for by an increase in pulmonary blood flow associated with an elevated resting metabolic rate. No dosage effect of SR was found. These findings support previous research that have demonstrated a decline in sympathetic activities after SR. For a further understanding of the effects of SR on hemodynamics, the changes in vestibulosympathetic reflex, baroreflex and vestibular/cerebellar respiratory responses warrants further study.

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REFERENCES

Balzano, S., Bergmann, M., Gilliland, M. A., Silva, J. E. and Rechtshaffen A. Effect of total sleep deprivation on 5'-deiodinase activity of rat brown adipose tissue. *Endocrinology*, 1990, 127: 882-890.

Bergmann, B. M., Everson, C. A., Kushida, C. A., Fang, V. S., Leitch, C. A., Schoeller, D. A., Refetoff, S. and Rechtschaffen, A. Sleep deprivation in the rat: V Energy use and mediation. *Sleep*, 1989, 12: 31-41.

Bonnet, M. H., Berry, R. B. and Arand, D. L. Metabolism during normal, fragmented, and recovery sleep. *J. Appl. Physiol.*, 1991, 71: 1112-1118.

Chen, H. I. Effects of 30-h sleep loss on cardiorespiratory functions at rest and in exercise. *Med. Sci. Sports Exerc.*, 1991, 23: 193-198.

Cooke, W. H., Hoag, J. B., Crossman, A. A., Kuusela, T. A., Tahvanainen, K. U. O. and Eckberg D. L. Human responses to upright tilt: a window on central autonomic integration. *J. Physiol.*, 1999, 517: 617-628.

Everson, C. A., Bergmann, B. M. and Rechtschaffen, A. Sleep deprivation in the rat: III. Total sleep deprivation. *Sleep*, 1989, 12: 13-21.

Everson, C. A., Gilliland, M. A., Kushida, C. A., Pilcher, J. J., Fang, V. S., Refetoff, S., Bergmann, B. M. and Rechtschaffen, A. Sleep deprivation in the rat: IX recovery. *Sleep*, 1989, 12: 60-67.

Fiorica, V., Higgins, E. A., Lampietro, P. F., Lategola, M. T. and Davis, A. W. Physiological responses of men during sleep deprivation. *J. Appl. Physiol.*,

1968, 24: 167-176.

Gotoh, T. M., Fujiki, N., Matsuda, T., Gao, S. and Morita, H. Roles of baroreflex and vestibulosympathetic reflex in controlling arterial blood pressure during gravitational stress in conscious rat. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, 2004, 286: R25-R30.

Harper, R. M. Sudden infant death syndrome: a failure of compensatory cerebellar mechanism? *Pediatr. Res.*, 2000, 48: 140-142.

Holmes, A. L., Burgess, H. J. and Dawson, D. Effects of sleep pressure on endogenous cardiac autonomic activity and body temperature. *J. Appl. Physiol.*, 2002, 92: 2578-84.

Kant, G. J., Genser, S. G., Throne, D. R., Pfalser, J. L. and Mougey, E. H. Effects of 72 hour sleep deprivation on urinary cortisol and indices of metabolism. *Sleep*, 1984, 7: 142-146.

Kato, M., Phillip, B. G., Sifurdsson, G. and Narkiewicz, K. Effects of sleep deprivation on neural circulatory control. *Hypertension*, 2000, 35: 1173-1175.

Kerman, I. A. and Yates, B. J. Regional and functional differences in the distribution of vestibular-sympathetic reflexes. *Am. J. Physiol.*, 1998, 275: R824-R835.

Koike, A., Itoh, H., Doi, M., Taniguchi, K., Marumo, F., Umehara, I. and Hiroe, M. Beat-to-beat evaluation of cardiac function during recovery from upright bicycle exercise in patients with coronary artery disease. *Am. Heart J.*, 1990, 120: 316-323.

Lagi, A., Cencetti, S., Corsoni, V., Georgiadis, D. and Bacilli, S. Cerebral vasoconstriction in vasovagal syncope: any link with symptoms? : a transcranial doppler study. *Circulation*, 2001, 104: 2694-2698.

Landis, C. A., Savage, M. V., Lentz, M. J. and Brengelmann, G. L. Sleep deprivation alters body temperature dynamics to mild cooling and heating not sweating threshold in women. *Sleep*, 1998, 21: 101-108.

Leproult, R., Copinschi, G., Buxton, O. and van Cauter, E. Sleep loss results in an elevation of cortisol levels the next evening. *Sleep*, 1997, 20: 865-870.

Lusardi, P., Mugellini, A., Preti, P., Zoppi, A., Derosa, G. and Fogari, R. Effects of a restricted sleep regimen on ambulatory blood pressure monitoring in normotensive subjects. *Am. J. Hypertens.*, 1996, 9: 503-505.

Lusardi, P., Zoppi, A., Preti, P., Pesce, R. M., Piazza, E. and Fogari, R. Effects of insufficient sleep on blood pressure in hypertensive patients: a 24-h study. *Am. J. Hypertens.*, 1999, 12: 63-68.

Lutherer, L. O., Lutherer, B. C., Dormer, K. J., Janssen, H. F. and Barnes, C.

D. Bilateral lesions of the fastigial nucleus prevent the recovery of blood pressure following hypotension induced by hemorrage or administration of endotoxin. *Brain Res.*, 1983, 269: 251-257.

Mancia, G. Autonomic modulation of the cardiovascular system during sleep. *N. Engl. J. Med.*, 1993, 329: 347-349.

Ogawa, Y., Kanbayashi, T., Saito, Y., Takahashi, Y., Kitajima, T., Takahashi, K., Hishikawa, Y. and Shimizu, T. Total sleep deprivation elevates blood pressure through arterial baroreflex resetting: a study with microneurographic technique. *Sleep*, 2003, 26: 986-989.

O,Hearn, E. and Molliver, M. E. The olivocerebellar projection mediates ibogaine-induced degeneration of Purkinije cells; a model of indirect, trans-synaptic excitotoxicity. *J. Neurosci.*, 1997, 17: 8828-8841.

Pagani, M., Lombardi, F., Guzzetti, S., Rimoldi, O., Furlan, R., Pizzinelli, P., Sandrone, G., Malfatto, G., Dell'Orto, S., Piccaluga, E., Turiel, M., Baselli, G., Cerutti, S. and Malliani, A. Power spectral analysis of heart rate and arterial pressure variabilities as a makers of sympathovagal interaction in man and conscious dog. *Circ. Res.*, 1986, 58: 178-193.

Pagani, M., Lucini, D., Rimoldi, O., Furlan, R., Piazza, S., and Biancardi, L. Mental Stress. *J. Ambul. Monitor.*,1992, 5: 235-244.

Palmblad, J., Akerstedt, T., Froberg, J., Melander, A. and von Schenck, H. Thyroid and adrenomedullary reactions during sleep deprivation. *Acta Endocrinologica*, 1979, 90: 233-239.

Shamsuzzaman, A. S. M., Caples, S. M. and Somers, V. K. Sleep deprivation and circulatory control: comment on Ogawa et al. Total sleep deprivation elevated blood pressure through arterial baroreflex resetting: a study with microneurographic technique. *Sleep*, 2003, 26: 986-989.

Somers, V. K., Dyken, M. E., Mark, A. L. and Abboud, F. Sympathetic-nerve activity during sleep in normal subjects. *N. Engl. J. Med.*, 1993, 328: 303-307.

Spiegel, K., Leproult, R. and Van Cauter, E. Impact of sleep debt on metabolic and endocrine function. *Lancet*, 1999, 354: 1435-1439.

Steenland, K., Lally, C. and Thun, M. Parity and coronary heart disease among women in the American Cancer Society CPS II population. *Epidemiology*, 1996, 7: 641-643.

Stringer, W., Hanson, J. and Wasserman, K. Cardiac output estimated noninvasively from oxygen uptake ($\dot{V}O_2$) during exercise. *J. Appl. Physiol.*, 1997, 82: 908-912.

Tilley, A. J. and Wilkinson, R. T. The effects of a restricted sleep regimen on the composition of sleep and on performance. *Psychophysiology*, 1984, 21:

406-412.

Vgntzas, A. N., Mastorakost, G., Bixler, E.O., Kales, A., Gold, P. W. and Chrousos, G. P. Sleep deprivation effects on the activity of the hypothalamic-pituitary and growth axes: potential clinical implications. *Clin. Endocrinol.*, 1999, 51: 205-215.

Wasserman, K., Vankessel A. and Burton, G. B. Interaction of physiological mechanisms during exercise. *J. Appl. Physiol.*, 1967, 22: 71-85.

Wasserman, K. Breathing during exercise. *N. Engl. J. Med.*, 1978, 298: 780-785.

Wasserman, K., Hansen, J. E., Sue, D. Y., Casaburi, R. and Whipp, B. J. Physiology of exercise In: Principles of exercise testing and interpretation: including pathophysiology and clinical application. Lippincott Williams & Wilkins 1999 (Third edition).

Xu, F., Owen, J. and Frazier, D. T. Cerebellar modulation of ventilatory response to progressive hypercapnia. *J. Appl. Physiol.*, 1994, 77: 1073-1080.

Xu, F., Owen, J. and Frazier, D. T. Hypoxic respiratory responses attenuated by ablation of the cerebellum or fastigial nuclei. *J. Appl. Physiol.*, 1995, 79: 1181-1189.

Yates, B. J., Siniaia, M. S. and Miller, A. D. Descending pathways necessary for vestibular influences on sympathetic and inspiratory outflow.*Am. J. Physiol.*, 1995, 268(6 Pt 2): R1381-R1385.

Yates, B. J. Vestibular influences on the autonomic nervous system. *Ann. N. Y. Acad. Sci.*, 1996, 781: 458-473.

Yates, B. J., Aoki, M., Burchill, P. and Bronstein, A. M. Cardiovascular responses elicited by linear acceleration in humans. *Exp. Brain Res.*, 1999, 125: 476-484.

FIGURE LEGENDS:

Figure 1. Comparison of systolic, mean and diastolic blood pressures (BP) (upper panel) and heart rate (HR) (bottom panel) at a resting, upright sitting position after normal sleep and after one- or two-days of sleep restriction. *p < 0.05, **p < 0.01, *** p < 0.005 after normal sleep versus after one- or two-days of sleep restriction. There was no significant difference in the above variables between one- and two-days of sleep restrictions.

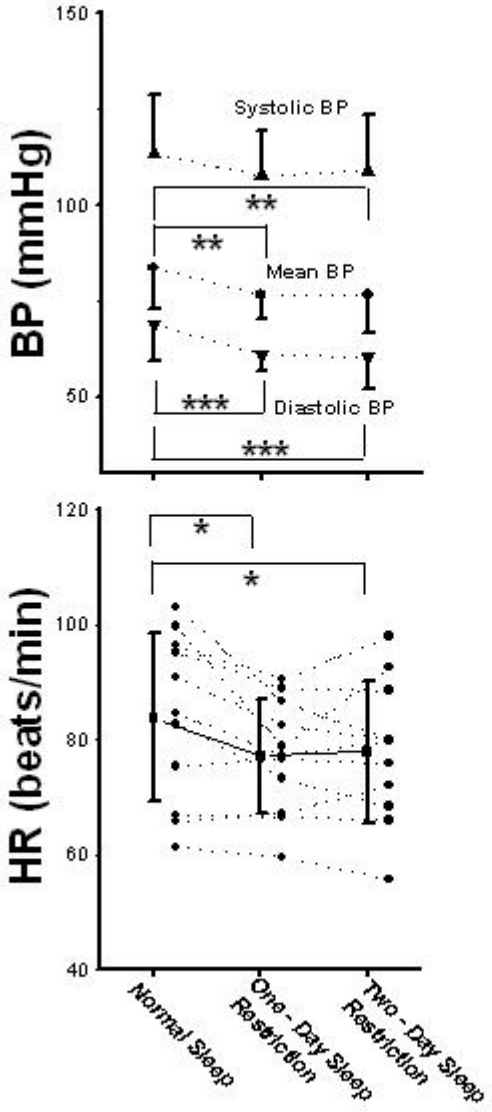

Figure 2. Comparison of minute O_2 uptake ($\dot{V}O_2$) (upper panel), and O_2 uptake per beat (O_2 pulse) (bottom panel) at a resting, upright sitting position after normal sleep and after one- or two-days of sleep restriction. *$p < 0.05$, *** $p < 0.005$ after normal sleep versus after one- or two-days of sleep restriction. There was no significant difference in the above variables between one- and two-days of sleep restrictions.

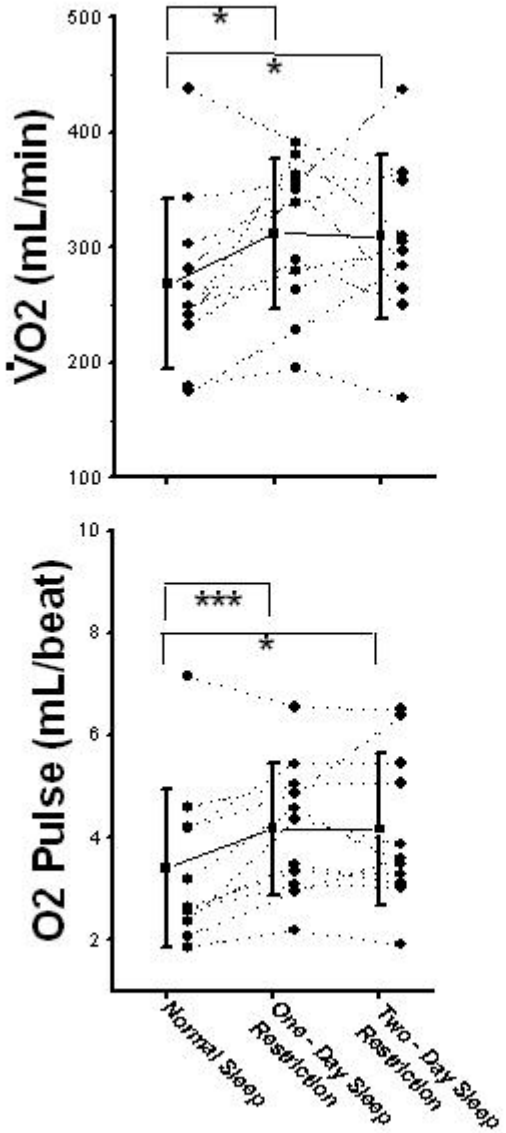

Figure 3. Comparison of equivalents for $\dot{V}O_2$ ($\dot{V}E/\dot{V}O_2$) (upper panel), and for $\dot{V}CO_2$ ($\dot{V}E/\dot{V}CO_2$) (bottom panel) at a resting, upright sitting position after normal sleep and after one- or two-days of sleep restriction. *p < 0.05 after normal sleep versus after one- or two-days of sleep restriction. There was no significant difference in the above variables between one- and two-days of sleep restrictions.

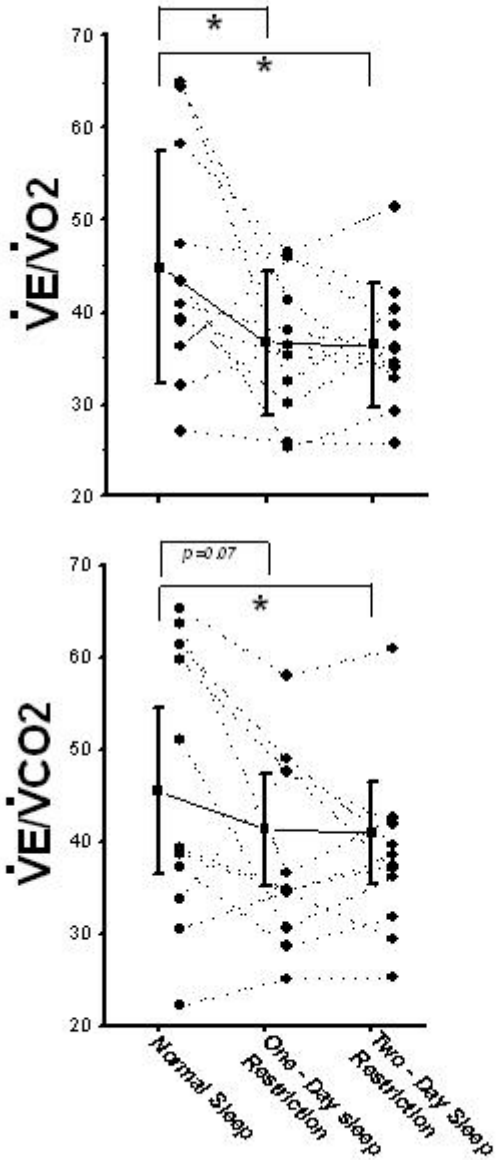

Table Comparison of gas changes and derivatives the morning after normal sleep, after one- and two-days of sleep restrictions

	Normal Sleep	*One-Day Sleep Restriction*	*Two-Day Sleep Restriction*
$\dot{V}O_2$, *mL/min*	268 ± 74	312 ± 65*	309 ± 71*
$\dot{V}CO_2$, *mL/min*	264 ± 79	273 ± 57	272 ± 57
O_2 Pulse, *mL/beat*	3.4 ± 1.6	4.2 ± 1.3***	4.2 ± 1.5*
RER	1.0 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
$\dot{V}E$, *L/min*	10.6 ± 2.7	10.7 ± 2.0	10.5 ± 1.6
Tidal Volume, *mL*	71 ± 27	62 ± 8	62 ± 10
Breath Frequency, *breaths/min*	16.4 ± 4.3	17.6 ± 3.1	17.0 ± 2.4
$\dot{V}E/\dot{V}O_2$	44.8 ± 12.7	36.7 ± 7.8*	36.5 ± 6.8*
$\dot{V}E/\dot{V}CO_2$	45.4 ± 9.0	41.3 ± 6.1	40.9 ± 5.5*
Pet O_2, *mm Hg*	117 ± 6	113 ± 4	113 ± 4
Pet CO_2, *mm Hg*	37 ± 3	38 ± 1	39 ± 2

Values are means ± SD. Definitions of Abbreviations: $\dot{V}O_2$ = minute O_2 uptake, $\dot{V}CO_2$ = minute CO_2 out put, O_2 Pulse = oxygen uptake per heart beat, RER = respiratory exchange ratio, $\dot{V}E$ = minute exhaled ventilatory volume, $\dot{V}E/\dot{V}O_2$ = the ventilatory equivalent for $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$ = the ventilatory equivalent for $\dot{V}CO_2$, Pet O_2 = end tidal O_2 partial pressure, Pet CO_2 = end tidal CO_2 partial pressure. * $p < 0.05$, ** $p < 0.01$ and ***$p < 0.005$ after normal sleep versus after one- or two-days of sleep restriction. No significant differences in above variables between one-day and two-days of sleep restrictions.