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Cardiovascular, Inflammatory and Metabolic Consequences of Sleep Deprivation

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Abstract

That insufficient sleep is associated with poor attention and performance deficits is becoming widely recognized. Fewer people are aware that chronic sleep complaints in epidemiological studies have also been associated with an increase in overall mortality and morbidity. This article summarizes findings of known effects of insufficient sleep on cardiovascular risk factors including blood pressure, glucose metabolism, hormonal regulation and inflammation with particular emphasis on experimental sleep loss, using models of total and partial sleep deprivation, in healthy individuals who normally sleep in the range of 7-8 hours and have no sleep disorders. These studies show that insufficient sleep alters established cardiovascular risk factors in a direction that is known to increase the risk of cardiac morbidity.

Keywords

inflammation; sleep deprivation; blood pressure; glucose metabolism; hormonal regulation

Self-reported short sleep duration and sleep complaints have long been associated with increased cardiovascular morbidity in epidemiological (1,2,3) and case-control studies (4). In a study of over 5,500 men and women, those sleeping <6 hours per night were 66% more likely to have hypertension than individuals obtaining between 7-8 hours per night (5), in another study this relationship was found for women and not men (6). Short sleep duration has been associated with increased risk for future coronary heart disease in women (7), impaired glucose tolerance in men and women (8), and the development of diabetes in women (9). Self-reported short sleep duration is also associated with metabolic syndrome markers in individuals between 30-54 years of age (10). Long sleep (>9h/night) has also been associated with increased risk for morbidity and mortality, but the relationship is

potentially obscured by illness or undiagnosed sleep or mood disorders, and is not the focus of the current review.

Effects of sleep deprivation on blood pressure

Several studies have found that experimental sleep deprivation leads to increased blood pressure (11,12,13,14), and even half a night of sleep loss has been reported to increase BP in subjects with hypertension or pre-hypertension (15).

Blood pressure is physiologically regulated via several mechanisms. Renal fluid filtration and reabsorption regulate blood volume and are under hormonal control, most importantly the renin-angiotensin system. Cardiac contractility (the force of cardiac ejection of blood into the systemic circulation), cardiac output (blood volume pumped in liters per minute) and peripheral vascular resistance are the other major determinants of measured blood pressure. These are under autonomic nervous control and linked to blood pressure via a feedback loop termed the baroreflex. The baroreflex involves a series of receptors, located in the heart itself as well as in the carotid artery and aortic arch, which sense blood pressure and relay information to the nucleus tractus solitarius in the medulla. If blood pressure needs to be adjusted, sympathetic or parasympathetic output then can influence cardiac contractility, heart rate and peripheral vascular resistance (16,17).

The autonomic nervous system output (for instance sympathetic nervous system activity measured directly by microneurography) can be plotted against variable blood pressures and the slope of the resulting curve has been termed baroreflex sensitivity. The intercept of the resulting curve with the abscissa (*x*-axis) has been used as an estimate of a baroreflex set point. Thus changing autonomic nervous activity at similar blood pressures suggest a central resetting of the baroreflex setpoint (18). An estimation of spontaneous baroreflex sensitivity can be achieved by calculating the square root of the ratio of low frequency heart rate variability to low frequency blood pressure variability (19). The dip in blood pressure seen during healthy sleep probably represents a change in set-point (20,21), and may serve a homeostatic function in blood pressure regulation. Sleep supports other homeostatic systems as well, including neuroendocrine and inflammatory systems. Increased sympathetic activation and decreased parasympathetic activation are seen during stress and increased work expenditure. Similar autonomic changes, consistent with a kind of stress response, may also be operating when sleep is of inadequate quantity and/or quality.

Staying awake beyond the normal 16-hour wake day involves exertion of energy, a fight against an accumulating sleep deficit, even when it is not accompanied by what most might consider stressful conditions such as extended normal work shifts or emergency operations. Motivation and circumstance influence the level of energy in the short term. Most of us have had the experience of being unable to sleep due to excitement or due to anxiety, and it seems like a greater effort to relax and permit sleep onset than it is to remain awake, but normally at least, resisting sleep in the context of a building sleep deficit takes work. To achieve this maintenance of wakefulness, against a building sleep deficit and a strong circadian drive for sleep, requires a good deal of motivation and effort, both of which are aided by social interaction. In order to maintain wakefulness, motivation must hold back the decline in optimism-sociability that occurs as a function of days of inadequate sleep amount (22). By one week of sleep reduction to about 50% of normal daily amount, self-reported optimism-sociability declines by about 10% compared to normal sleep conditions. It is reasonable to expect that the autonomic system is activated during the resisting phase of an extended vigil.

Sympathetic activation

Based on controlled chronobiological studies, Burgess and colleagues (23) found that sleep was more important for sympathetic nervous system regulation of the heart in comparison with the parasympathetic system that appeared to be more under circadian control. In that study, posture and light were strictly controlled, sympathetic nervous system activity was assessed using the pre-ejection period estimated from impedance cardiography indices (estimating isovolumic contraction time) and parasympathetic activity was estimated by the respiratory sinus arrhythmia (based on spectral analysis of beat to beat cardiac intervals). These investigators reported that sleep was important for the diurnal rhythm of the pre-ejection period, but not the respiratory sinus arrhythmia.

BP could be increased during sleep deprivation due to increased sympathetic outflow to the heart or periphery, due to changes in baroreflex sensitivity, due to baroreflex resetting to a higher level, or a combination of these factors. The question as to whether the increase in BP found in several investigations of sleep reduction or deprivation is due to central sympathetic mechanisms has been addressed, but the conditions of deprivation have strong influences on the results. In addition, mechanisms that maintain cardiovascular systems may respond differently depending on experimental conditions.

Kato et al., (13) examined blood pressure, heart rate, forearm vascular resistance, and muscle sympathetic nerve activity, after normal sleep and after a night of recumbent sleep deprivation in 8 healthy middle-aged participants. They measured the response to 4 stressors following sleep deprivation compared with control. These investigators found that while forearm vascular resistance and plasma catecholamines were not affected by this duration of sleep loss, mean arterial BP did increase but muscle sympathetic nerve activity decreased. The stress responses tested did not change due to deprivation. Ogawa et al., (12) subsequently confirmed the findings of increased BP and decreased muscle sympathetic nerve activity following a night of recumbent sleep deprivation in a group of 6 young male participants. In addition, these investigators found that the arterial baroreflex was reset upwards by 12 mmHg towards a higher blood pressure by a single night of sleep deprivation.

Holmes et al., (24) published a study in which subjects were lying in bed awake for either 30h or 6h before being permitted to sleep. HR, cardiac pre-ejection period assessed via impedance cardiography as an estimate of sympathetic tone, and respiratory sinus arrhythmia as an estimate of parasympathetic tone, were monitored during 6 hours or 30 hours of sleep deprivation and the initial 2 hours of a sleep opportunity following the period of sleep deprivation in twelve healthy subjects. During prolonged sleep deprivation respiratory sinus arrhythmia was not altered but HR decreased and cardiac pre-ejection period lengthened as a result of decreased cardiac sympathetic activity. This pattern was maintained into the recovery sleep phase of the study. Together these studies suggest that increased BP is due to baroreflex setpoint change and that sympathetic outflow is dampened as a protective response. However, it is very difficult to maintain wakefulness during recumbency when sleep pressure is strong, and furthermore the extent of wakefulness maintained is not clear in these reports. These study conditions cannot approximate the real-world effects of sleep loss on cardiovascular functioning.

Two studies of sleep deprivation that were carried out with participants avoiding recumbent posture during the vigil period show that sympathetic outflow is indeed increased. In a study involving 6 nights of partial sleep deprivation, Spiegel and colleagues (25) found that sympathovagal balance was elevated by sleep loss, during the morning through mid-day hours. Zhong et al. (26) studied HR, BP and HRV and baroreflex sensitivity computed from

HRV and BP variability data in 18 healthy subjects between 19-36 yrs of age, undergoing continuous sleep deprivation under conditions of controlled ambient temperature and fluid intake. Baseline measures during supine resting, seated resting and seated with cognitive testing were made at 9 pm on baseline and 12, 24 and 36 hours later. When baseline seated physiological testing was measured 24 hours later, at the same time of day, after approximately 39 hours of wakefulness, HR, low frequency heart rate variability and BP variability were all increased, and baroreflex sensitivity was decreased. BP was not changed. Subsequent testing at 9am following an additional 12 hours of nocturnal wakefulness is not as easily interpreted since there were no baseline measures at that time of day. Nonetheless, low frequency BP variability was elevated throughout deprivation and in all testing conditions studied.

Investigations have used different methodologies and experimental conditions, and also show differing results. As shown in the study by Zhong and colleagues discussed above, the sympathetic nervous system and BP are significantly modulated by the activities undertaken and environmental conditions of studies. Body posture, ambient temperature, emotional stress, cognitive and physical workload, fluid levels and food and salt intake influence regulating factors such as hormones and catecholamines that control blood pressure and can exert effects on study outcomes. Studies that show decreased sympathetic activity involved recumbent posture throughout the deprivation period, and deprivation was necessarily relatively short for this reason. Studies investigating cardiovascular changes during sleep deprivation carried out under non-recumbent conditions support the hypothesis that sleep deprivation involves increased sympathetic cardiac and BP modulation and decreased baroreflex sensitivity.

Endocrine/metabolic changes associated with sleep loss

Anabolic hormones are altered by sleep deprivation. Growth hormone (GH) reaches its daily maximum in the first half of the sleep period, and in healthy middle-aged men, up to about 70% of the daily GH secretion occurs during this window of time. During sleep deprivation, the sleep-associated GH pulse is substantially dampened or abolished. In addition to signs of hypothalamic-pituitary-adrenal axis activation, sleep deprivation also alters the output of metabolic hormones as measured in peripheral circulation. As is described elsewhere in this issue, glucose metabolism is slowed during sleep deprivation (both total (27) and partial sleep deprivation (28)). Thus, insufficient sleep may be a potentially important contributing mechanism in the clinical development of insulin resistance, increased accrual of adipocytes and resulting elevated inflammatory mediators.

Leptin, an adipocyte hormone that signals satiety to the brain, is reduced in diurnal rhythm amplitude (28) and peak amount (29) as measured in peripheral circulation during acute total and sustained partial sleep deprivation. Ghrelin, a hormone that signals hunger to the brain, and subjective appetite is increased during partial sleep deprivation (29). The combination of slowed metabolism produced by sleep deprivation, and increased appetite may theoretically lead to weight gain and may contribute to the increasing prevalence of obesity and the development of the metabolic syndrome.

Sleep plays a role in thermoregulation and sleep deprivation not only represents loss of sleep, it represents a reduction in the normal nocturnal drop in both body temperature and BP. In concert with this drop in temperature, the TSH level is elevated during sleep deprivation (30,31,32,33,34). Some of these studies have also found increased free thyroid hormones T3 and T4 (30,31,32). The elevations seen in short term experimental sleep deprivation studies are without clinical sequelae and resolve quickly with recovery sleep. However, the thyroid is a major regulator of metabolic rate, modulating O2 consumption,

heart contractility and cardiac output, and affects all aspects of carbohydrate metabolism. In addition, it raises the rate at which the gastrointestinal tract absorbs glucose, which increases insulin resistance. The small TSH changes described during sleep deprivation, if chronic, may nonetheless contribute to the development of disease.

Findings are mixed with respect to increased stress markers during sleep deprivation. Elevations in cortisol have been found during total acute sleep deprivation in the late afternoon and into the early nighttime hours, when cortisol is typically at its nadir (35,36,37), and an elevation in afternoon cortisol levels has also been reported in partial sleep deprivation (25). In sleep deprivation studies, catecholamine results have been conflicting. In an ambulatory extended workday study, Tochikubo et al., (11) found urinary norepinephrine increased by 35% at night during sleep deprivation and 15% over the 24h day. Other investigators have reported increased urinary norepinephrine (15) and increased circulating epinephrine and norepinephrine (38) with half a night of sleep deprivation. However, others found no major increase in catecholamines due to sleep deprivation (39,30,40), but as with the blood pressure studies, posture and other study conditions are likely important.

Sleep loss, inflammation and cardiovascular disease

What causes inflammation in asymptomatic individuals that later go on to develop cardiovascular disease? A number of factors can lead to elevated inflammatory mediators and markers, including infection and injury. Adiposity, particularly visceral adipocity, contributes directly to the production of IL-6 and other inflammatory mediators, which in turn stimulate production of CRP. Hypoxia is a hallmark of the sleep apnea syndrome and is strongly associated with elevations in inflammatory mediators. Could insufficient amount or inadequate quality of sleep contribute to the development of an elevated inflammatory state in individuals without sleep disorders or CVD? During experimental sleep deprivation of healthy participants, white blood cells and other markers of inflammation show increases in the range of those associated with the future development of cardiovascular disease. Taken together, these findings raise the question, could insufficient sleep duration, over years perhaps, contribute to the development of sustained inflammation and increased risk for cardiovascular disease?

A relationship between inflammation and cardiovascular disease has long been recognized. In the 1920s it was noted that patients with congestive heart failure also had high leukocyte numbers (41), and this relationship was confirmed some years later in a case-controlled study (42). More recently, a number of prospective studies have identified an association between risk, in asymptomatic individuals, for the development of cardiovascular disease and leukocyte counts. While risk estimates vary considerably from study to study, a meta-analysis suggests that the overall average risk associated with elevated WBC is about 1.5 (43). Furthermore, the risk is thought to be independently associated with WBC, after other significant factors such as smoking and obesity are taken into account.

IL-6 is produced by the monocyte/macrophage leukocyte cell line and by activated endothelial cells lining vascular and lymph beds. In addition, adipocytes are also known to produce IL-6. IL-6 is a potent stimulator of CRP production in liver, and recent data suggest that it is also produced in arterial smooth muscle cells (44) and vascular endothelial cells (45). While IL-6 is predictive of the development of cardiovascular disease (46), CRP has an advantage in that it is more stable, with a much longer half-life (47); and is without diurnal rhythm (48). CRP is an independent predictor of a first cardiovascular event in asymptomatic individuals and is furthermore associated with adversity of that event (49).

Inflammatory mediators are increased by shortened sleep or sleep deprivation

Monocytes and neutrophils, phagocytic cells in peripheral circulation, are elevated during acute sleep deprivation (50,51,52,53). IL-6 is also produced by adipocytes and by endothelial cells. Interestingly, IL-6 and CRP have both been found to increase during acute total sleep deprivation (54,13) and also during sleep restricted to half the normal daily amount for 10 days (13,55) and in one study, even when sleep is reduced by 25% of the normal amount for 8 nights (56).

The increases in IL-6 are very small and negative results have also been reported. Frey et al., (57) looking at a single night of acute sleep loss under constant conditions of body posture, light levels and nutritional intake, failed to see an increase, and in fact reported a *decrease* in IL-6 and CRP. Since IL-6 is produced by many cells in the periphery, including endothelial cells, factors that affect the activation of those cells, for example vasoconstriction and blood pressure, are likely to be important determinants of the response to sleep loss.

Some studies have reported a diurnal rhythm for IL-6 in peripheral circulation, with a peak during the nocturnal phase (58,59), and Redwine and colleagues found that the nocturnal increase could be delayed with the delay of the onset of the bed period by 5 hours (60). The IL-6 association with sleepiness or sleep pressure has been demonstrated using very different research approaches. For example, in studies of human challenge with IL-6 and with endotoxin, IL-6 levels are associated with various indices of sleepiness (61,62). In obesity, excessive daytime sleepiness is associated with sleepiness with or without concordant sleep apnea (63), and studies have confirmed the elevation of inflammatory and coagulatory mediators in sleep apnea (see other chapters in this issue)

Human sleep loss also affects the TNF system. In a study of mild sleep loss (two hours per night for seven nights) in healthy men and women, men showed elevations of TNF-alpha as a consequence of sleep restriction, whereas women did not show this change (56). In another study involving men who were sleep restricted to two 2h naps per day for 4 days, Shearer et al., (54) found no increase in TNF-alpha or its receptors. In another recent study involving men and women who underwent sleep reduction for 10 nights, there were no significant changes seen in TNF-alpha or its soluble p55 receptor (55). As yet incompletely understood individual differences in vulnerability to sleep loss may underlie these discrepancies, or perhaps subtle but important differences in methods. While the TNF family sometimes responds to partial sleep deprivation, there is evidence that the type I (but not type 2) soluble TNF receptor is influenced by acute complete sleep loss (54). Nonetheless, following a single night of sleep reduced by 50%, Irwin and colleagues (64) showed an increase in monocyte production of IL-6 and TNF-a messenger RNA.

One of the explanations for why inflammatory mediators are elevated in cardiovascular disease is that the increased blood pressure increases endothelial shear stresses, resulting in endothelial production of inflammatory mediators (65). During sleep, endothelial markers drop to their lowest point in the day (66), coinciding with the nocturnal dip in blood pressure. Both acute total sleep deprivation and prolonged partial sleep deprivation ((~50% of normal sleep duration for 10 days) (67)) lead to blood pressure elevations over control in human subjects undergoing controlled physiological studies. In addition, E-selectin and ICAM-1 have been reported to increase under conditions of sleep deprivation (57,68). These findings may be interpreted as supporting the hypothesis that activated vasculature, related to elevated BP, leads to activation of an inflammatory cascade. As well, autonomic system activation may contribute to elevated inflammation via multiple pathways. Catecholamine elevation is associated with increased inflammatory mediators (69), and in the in vivo

model, norepinephrine can stimulate production of inflammatory mediators including IL-6 and TNF-alpha (70,71).

Short-term physiological studies have shown that insufficient and/or inadequate sleep are associated with slowed glucose metabolism and an increase in inflammatory mediators, suggesting that sleep is an important homeostatic regulator of factors contributing to the development of the metabolic syndrome and of cardiovascular disease. Although short sleep duration has been linked with increased risk for the development of cardiovascular disease and also development of type-2 diabetes, few epidemiological studies have examined the relationship between habitual short sleep duration and inflammatory status. In one study of children, a significant relationship was found between high sensitivity CRP levels and sleep duration, even after statistically removing the variance attributable to age, sex and BMI (72). A cross-sectional study of adults in the Wisconsin Sleep Cohort adults failed to find a relationship between CRP concentration and habitual sleep duration or CRP and total sleep time on a laboratory based sleep study (73). Given that sex is an important independent variable in the association between sleep duration and hypertension (6), it may be that there are sex differences in the inflammatory response to insufficient or short sleep duration. Additional studies based on samples large enough to enable examination of individual differences, that investigate the relationship between sleep duration/quality with inflammatory status and its relationship to future development of cardiovascular disease, would be an important contribution to the field.

In short-term studies of both acute sleep deprivation, and partial sleep deprivation, inflammatory mediators have been seen to rise, but most of these studies have been performed on men (50,51,53,54,14). Of the few studies investigating the inflammatory response to sleep loss that have included women (14,55,56,57), sex differences have not been reported, but studies have not been powered to test for these differences. One notable exception has been a study by Vgontzas et al., (56). These authors studied 12 men and 13 women and found a significant increase in TNF-α following a week of sleep restriction of approximately 25% habitual duration, in men but not women. IL-6 on the other hand, was increased in both men and women. A recent study suggested that a single night of short sleep (4 h) is associated with activation of NF-κB, in women but not men (74). Another recent study investigated the relationship between self-reported symptoms of sleep disturbance and inflammatory mediators and coagulatory factors in healthy men and women found that sleep disturbance was related to elevations in women but again, not men. (75). Preliminary findings are suggesting, that while men and women both do show inflammatory responses in studies of acute sleep deprivation, there may be individual differences in the vulnerability for developing short-sleep-induced inflammation, both in the short and long term. Once it is developed, there may be further individual differences in tolerance to increased inflammation and resistance to the development of disease.

Summary and future directions

Autonomic functioning, inflammatory and coagulatory mediators and hormonal profiles are all altered during controlled sleep deprivation studies. The mechanism of this increase is not known, and certainly is related to the strain of maintaining wakefulness under conditions of an accumulating sleep deficit, and at times when the biological clocks are primed for sleep. It is not known if these changes are short-lived and these systems are able to adapt over time.

The available experimental data, as reviewed here, suggest that with short term sleep deprivation blood pressure, inflammation, autonomic tone and hormones all are altered in a direction that is recognized to contribute to the development of cardiovascular disease, most

importantly, atherosclerosis. The changes seen with experimental models of total and partial sleep deprivation are mild, usually subclinical, and resolve quickly with recovery sleep. Nevertheless the magnitude of change is similar to that seen in profiles predicting future CVD risk, and therefore are worthy of investigation. It is reasonable to hypothesize that chronic under-sleeping may contribute to the establishment of basal elevations in inflammatory mediators and coagulatory factors, thereby priming otherwise healthy individuals for development of disease. This is an important question for public health and health risk management in aging and warrants further attention.

Future studies are needed to investigate the relationship between short term acute and more prolonged partial sleep deprivation under controlled settings, and sex and age differences in physiological responses to sleep loss challenge. In addition, the relationships between autonomic, inflammatory, coagulatory and metabolic and hormonal changes in individuals chronically under-sleeping in their daily lives, and interventions to investigate the reversibility of these changes through sleep extension, for example, are needed. At the physiological level as well as in field and epidemiological studies, the relationship between vulnerability to sleep loss and individual differences needs to be investigated with a multidisciplinary approach so that the consequences of sleep loss can be better understood at a systems level, so that individualized approaches to preventative strategies can be tested to reduce future cardiovascular and metabolic syndrome related disease risk.

References

1. Appels A, de Yos Y, van Diest R, et al. Are sleep complaints predictive of future myocardial infarction? Activitas Nervosa Superior. 1987; 29:147–151. [PubMed: 3661100]
2. Eaker ED, Pinsky J, Castelli WP. Myocardial infarction and coronary death among women: Psychosocial predictors from a 20-year follow-up of women in the Framingham study. Am J Epidemiol. 1992; 135:854–864. [PubMed: 1585898]
3. Schwartz SW, Cornoni-Huntley J, Cole SR, Hays JC, Blazer DG, Schocken D. Are sleep complaints an independent risk factor for myocardial infarction? Ann Epidemiol. 1998; 8:384–92. [PubMed: 9708874]
4. Liu Y, Tanaka H. Overtime work, insufficient sleep, and risk of non-fatal acute myocardial infarction in Japanese men. Occup Environ Med. 2002; 59:447–51. [PubMed: 12107292]
5. Gottlieb DJ, Punjabi NM, Newman AB, et al. Association of sleep time with diabetes mellitus and impaired glucose tolerance. Arch Intern Med. 2005; 165:863–868. [PubMed: 15851636]
6. Cappuccio FP, Stranges S, Kandala N, Miller MM, Taggart FM, Kumari M, Ferrie JE, Shipley MJ, Brunner EJ, Marmot MG. Gender-specific associations of short sleep durations with prevalent and incident hypertension. The Whitehall II Study. Hypertension. 2007; 50:693–700. [PubMed: 17785629]
7. Ayas NT, White DP, Manson JE. A prospective study of sleep duration and coronary heart disease in women. Arch Intern Med. 2003; 163:205–209. [PubMed: 12546611]
8. Gottlieb DJ, Redline S, Nieto FJ, et al. Association of usual sleep duration with hypertension: The sleep heart health study. Sleep. 2006; 29:1009–14. [PubMed: 16944668]
9. Ayas NT, White DP, Manson JE, et al. A prospective study of sleep duration and type II diabetes in women. Diabetes Care. 2003; 26(2):380–4. [PubMed: 12547866]
10. Hall MH, Muldoon MF, Jennings JR, Buysse DJ, Flory JD, Manuck SB. Self-reported sleep duration is associated with the metabolic syndrome in midlife adults. Sleep. 2008; 31:635–643. [PubMed: 18517034]
11. Tochikubo O, Ikeda A, Miyajima E, et al. Effects of insufficient sleep on blood pressure monitored by a new multibiomedical recorder. Hypertension. 1996; 27:1318–24. [PubMed: 8641742]
12. Ogawa Y, Kanbayashi T, Saito Y, et al. Total sleep deprivation elevated blood pressure through arterial baroreflex resetting: a study with microneurographic technique. Sleep. 2003; 26:986–989. [PubMed: 14746379]

13. Kato M, Phillips BG, Sigurdsson G, et al. Effects of sleep deprivation on neural circulatory control. Hypertension. 2000; 35:1173–1175. [PubMed: 10818083]
14. Meier-Ewert HK, Ridker PM, Nader R, et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. JACC. 2004; 43:678–683. [PubMed: 14975482]
15. Lusardi P, Zoppi A, Preti P. Effects of insufficient sleep on blood pressure in hypertensive patients. A 24-h study. Am J Hypertens. 1999; 12:63–8. [PubMed: 10075386]
16. Cowley AW. Long term control of arterial blood pressure. Physiol Rev. 1992; 72:231–300. [PubMed: 1731371]
17. Hamill, RW. Peripheral autonomic nervous system. In: Robertson, D.; Low, PA.; Polinsky, RJ., editors. Primer on the autonomic nervous system. San Diego, CA: Academic Press; 1996. p. 12-25.
18. Eckberg, DL. High- and low pressure baroreflexes. In: Robertson, D.; Low, PA.; Polinsky, RJ., editors. Primer on the autonomic nervous system. San Diego, CA: Academic Press; 1996. p. 59-65.
19. Persson PB, DiRienzo M, Castiglione P, Cerutti C, Pagani M, Honzikova N, Akselrod S, Parati G. Time versus frequency domain techniques for assessing baroreflex sensitivity. J Hypertens. 2001; 19:1699–1705. [PubMed: 11593087]
20. Bursztyn M, Mekler J, Wachtel N, Ben-Ishay D. Siesta and ambulatory blood pressure monitoring. Comparability of the afternoon nap and night sleep. Am J Hypertens. 1994; 7:217–221. [PubMed: 8003271]
21. Cortelli P, Pierangeli G, Provini F, et al. Blood Pressure Rhythms in Sleep Disorders and Dysautonomia. Ann N Y Acad Sci. 1996; 783:113–31. [PubMed: 8853637]
22. Haack M, Mullington JM. Sustained Sleep Restriction Reduces Emotional and Physical Well-Being. Pain. 2005; 119:56–64. [PubMed: 16297554]
23. Burgess HJ, Trinder J, Kim Y, Luke D. Sleep and circadian influences on cardiac autonomic nervous system activity. Am J Physiolo. 1997; 273:H1761–H1768. Heart Circ Physiol 42.
24. Holmes AL, Burgess HJ, Dawson D. Effects of sleep pressure on endogenous cardiac autonomic activity and body temperature. J Appl Physiol. 2002; 92:2578–2584. [PubMed: 12015376]
25. Spiegel K, Leproult R, van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet. 1999; 354:1435–9. [PubMed: 10543671]
26. Zhong X, Hilton HJ, Gates GJ, et al. Increased sympathetic and decreased parasympathetic cardiovascular modulation in normal humans with acute sleep deprivation. J Appl Physiol. 2005; 98:2024–32. [PubMed: 15718408]
27. Gonzalez-Ortiz M, Martinez-Abundis E, Balcazar-Munoz BR. Effect of sleep deprivation on insulin sensitivity and cortisol concentration in healthy subjects. Diabetes Nutr Metab. 2000; 13:80–3. [PubMed: 10898125]
28. Mullington JM, Chan JL, Samaras J, Szuba MP, Meier-Ewert HK, Van Dongen HPA, Price N, Dinges DF, Mantzoros CS. Sleep loss reduces the amplitude of the diurnal leptin rhythm in healthy men. J Neuroendocrinol. 2003; 15:851–4. [PubMed: 12899679]
29. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Ann Intern Med. 2004; 141:846–50. [PubMed: 15583226]
30. Palmblad J, Akerstedt T, Froberg J, Melander A, von Schenck H. Thyroid and adrenomedullary reactions during sleep deprivation. Acta Endocrinol. 1979; 90:233–9. [PubMed: 419915]
31. Gary KA, Winokur A, Douglas SD, et al. Total sleep deprivation and the thyroid axis: effects of sleep and waking activity. Aviat Space Environ Med. 1996; 67:513–9. [PubMed: 8827131]
32. Radomski MW, Hart LE, Goodman JM, Plyley MJ. Aerobic fitness and hormonal responses to prolonged sleep deprivation and sustained mental work. Aviat Space Environ Med. 1992; 63:101–6. [PubMed: 1347679]
33. Goichot B, Brandenberger G, Saini J, et al. Nycthemeral patterns of thyroid hormones and their relationships with thyrotropin variations and sleep structure. J Endocrinol Invest. 1994; 17:181–7. [PubMed: 8051340]

34. Sadamatsu M, Kato N, Iida H, Takahashi S, Sakaue K, Takahashi K, Hashida S, Ishikawa E. The 24-hour rhythms in plasma growth hormone, prolactin and thyroid stimulating hormone: effect of sleep deprivation. J Neuroendocrinol. 1995; 7:597–606. [PubMed: 8704733]
35. Mullington J, Hermann D, Holsboer F, Pollmächer T. Age-dependent suppression of nocturnal growth hormone levels during sleep deprivation. Neuroendocrinology. 1996; 64:233–241. [PubMed: 8875441]
36. Späth-Schwalbe E, Uthgenannt D, Voget G, et al. Corticotropin-releasing hormone-induced adrenocorticotropin and cortisol secretion depends on sleep and wakefulness. J Clin Endocrinol Metab. 1993; 77:1170–1173. [PubMed: 8077308]
37. Weitzman ED, Zimmerman JC, Czeisler CA, Ronda J. Cortisol secretion is inhibited during sleep in normal man. J Clin Endocrinol Metab. 1983; 56:352–8. [PubMed: 6822642]
38. Irwin MR, Thompson J, Miller C, Gillin JC, Ziegler M. Effects of sleep and sleep deprivation on catecholamine and interleukin- 2 levels in humans: clinical implications. J Clin Endocrinol Metab. 1999; 84:1979–85. [PubMed: 10372697]
39. Akerstedt T, Froberg JE. Sleep and stressor exposure in relation to circadian-rhythms in catecholamine excretion. Biol Psychol. 1979; 8:69–80. [PubMed: 465621]
40. Schmid SM, Hallschmid M, Jauch-Chara K, et al. Sleep loss alters basal metabolic hormone secretion and modulates the dynamic counterregulatory response to hypoglycemia. J Clin Endo & Metab. 2007; 92:3044–3051.
41. Keefer CS, Resnik WH. Angina pectoris: a syndrome caused by anoxemia of the myocardium. Arch Intern Med. 1928; 41:769–807.
42. Friedman GD, Klatsky AL, Siegelaub AB. The leukocyte count as a predictor of myocardial infarction. N Engl J Med. 1974; 290:1275–8. [PubMed: 4827627]
43. Danesh J, Collins R, Appleby P, et al. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analysis of prospective studies. JAMA. 1998; 279:1477–82. [PubMed: 9600484]
44. Calabro P, Willerson JT, Yeh ETH. Inflammatory cytokines stimulated C-reactive protein production by human coronary artery smooth muscle cells. Circulation. 2003; 108:1930–2. [PubMed: 14530191]
45. Singh P, Hoffmann M, Wolk R, Shamsuzzaman AS, Somers VK. Leptin induces C-reactive protein expression in vascular endothelial cells. Arterioscler Thromb Vasc Biol. 2007; 27:e302–7. [PubMed: 17615382]
46. Ridker PM, Rifai N, Stampfer MJ, et al. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation. 2000; 101:1767–72. [PubMed: 10769275]
47. Vigushin DM, Pepys MB, Hawkins PN. Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. J Clin Invest. 1993; 91:1351–7. [PubMed: 8473487]
48. Meier-Ewert HK, Ridker PM, Rifai N, Price N, Dinges DF, Mullington JM. Absence of a diurnal variation of C-reactive protein concentration in healthy human subjects. Clin Chem. 2001; 47:426–30. [PubMed: 11238292]
49. Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation. 2001; 103:1813–8. [PubMed: 11282915]
50. Kuhn E, Brodan V, Brodanová M, Rysánek K. Metabolic reflection of sleep deprivation. Act Nerv Super (Praha). 1969; 11:165–74. [PubMed: 5798779]
51. Dinges DF, Douglas SD, Zaugg L, et al. Leukocytosis and natural killer cell function parallel neurobehavioral fatigue induced by 64 hours of sleep deprivation. J Clin Invest. 1994; 93:1930–1939. [PubMed: 7910171]
52. Boyum A, Wiik P, Gustavsson E, et al. The effect of strenuous exercise, calorie deficiency and sleep deprivation on white blood cells, plasma immunoglobulins and cytokines. Scand J Immunol. 1996; 43:228–35. [PubMed: 8633203]
53. Born J, Lange T, Hansen K, et al. Effects of sleep and circadian rhythm on human circulating immune cells. J Immunol. 1997; 158:4454–4464. [PubMed: 9127011]

54. Shearer WT, Reuben JM, Mullington J, et al. Soluble tumor necrosis factor-alpha receptor I and IL-6 concentrations in humans subjected to the sleep deprivation model of space flight. J Allergy Clin Immunol. 2001; 107:165–170. [PubMed: 11150007]
55. Haack M, Sanchez E, Mullington JM. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. Sleep. 2007; 30:1145–1152. [PubMed: 17910386]
56. Vgontzas AN, Zoumakis E, Bixler EO, Lin HM, Follett H, Kales A, Chrousos GP. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. J Clin Endocrinol & Metab. 2004; 89:2119–2126. [PubMed: 15126529]
57. Frey DJ, Fleshner M, Wright KP. The effects of 40 hours of total sleep deprivation on inflammatory markers in healthy young adults. Brain Behav Immun. 2007; 21:1050–7. [PubMed: 17524614]
58. Bauer J, Hohagen F, Ebert T. Interleukin-6 serum levels in healthy persons correspond to the sleep-wake cycle. Clin Invest. 1994; 72:315.
59. Vgontzas AN, Zoumakis M, Papanicolaou DA, et al. Chronic insomnia is associated with a shift of interleukin-6 and tumor-necrosis factor secretion from nighttime to daytime. Metabolism. 2002; 51:887–92. [PubMed: 12077736]
60. Redwine L, Hauger RL, Gillin JC, Irwin M. Effects of sleep and sleep deprivation on interleukin-6, growth hormone, cortisol, and melatonin levels in humans. J Clin Endocrinol Metab. 2000; 85:3597–603. [PubMed: 11061508]
61. Späth-Schwalbe E, Hansen K, Schmidt F, et al. Acute effects of recombinant human IL-6 on endocrine and central nervous sleep functions in healthy men. J Clin Endocrinol Metab. 1998; 83:1573–9. [PubMed: 9589658]
62. Hermann DM, Mullington J, Hinze-Selch D, Schreiber W, Galanos C, Pollmächer T. Endotoxin-induced changes in sleep and sleepiness during the day. Psychoneuroendocrinology. 1998; 23:427–37. [PubMed: 9802118]
63. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral adiposity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab. 2000; 85:1151–8. [PubMed: 10720054]
64. Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. Arch Intern Med. 2006; 166:1756–1762. [PubMed: 16983055]
65. Chae CU, Lee RT, Rifai N, Ridker PM. Blood pressure and inflammation in apparently healthy men. Hypertension. 2001; 38:399–403. [PubMed: 11566912]
66. Mullington JM, Haack M, Rifai N. Cellular adhesion molecules (ICAM and VCAM), E- and P-selectins show diurnal rhythms with nadirs during sleep. J Sleep Res. 2004; 14:s519.
67. Broussard J, Haack M, Serrador J, Mullington J. Effects of sleep restriction on blood pressure. Sleep. 2004; 27:A171.
68. Sanchez A, Haack M, Tóth M, Serrador J, Mullington JM. Effects of sleep deprivation on blood pressure and vascular cellular adhesion molecules. Sleep. 2008; 31:A137.
69. Papanicolaou DA, Petrides JS, Tsigos C, Bina S, Kalogeras KT, Wilder R, Gold PW, Deuster PA, Chrousos GP. Exercise stimulates interleukin-6 secretion - inhibition by glucocorticoids and correlation with catecholamines. Am J Physiol Endocrinol Metab. 1996; 271:E601–E605.
70. Van Gool J, Van Vugt H, Helle M, Aarden LA. The relation among stress, adrenaline, interleukin-6 and acute phase proteins in the rat. Clinical Immunology and Immunopathology. 1990; 57:200–10. [PubMed: 1698583]
71. DeRijk RH, Boelen A, Tilders FJ, et al. Induction of plasma interleukin-6 by circulating adrenaline in the rat. Psychoneuroendocrinology. 1994; 19:155–63. [PubMed: 8190835]
72. Larkin EK, Rosen CL, Kirchner HL, Storfer-Isser A, Emancipator JL, Johnson NL, Zambito AM, Tracy RP, Jenny NS, Redline S. Variation of C-reactive protein levels in adolescents: association with sleep-disordered breathing and sleep duration. Circulation. 2005; 111(15):1978–84. [PubMed: 15837952]

73. Taheri S, Austin D, Lin L, Nieto FJ, Young T, Mignot E. Correlates of serum C-reactive protein (CRP)--no association with sleep duration or sleep disordered breathing. Sleep. 2007; 30:991–6. [PubMed: 17702268]

74. Irwin MR, Wang M, Ribeiro D, et al. Sleep loss activates cellular inflammatory signaling. Biological Psychiatry. in press.

75. Suarez EC. Self-reported symptoms of sleep disturbance and inflammation, coagulation, insulin resistance and psychosocial distress: Evidence for gender disparity. Brain, Behavior and Immunity. 2008; 22:960–8.