Inflammation and Sleep in Healthy Individuals

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**Study Objectives:** Inflammation is relatively common in individuals with a sleep disorder and is associated with quality of sleep. The purpose of this study was to examine whether inflammation is associated with quality of sleep in healthy individuals.

**Design & Setting:** Observational study in a General Clinical Research Center.

**Participants:** This study characterized inflammation and polysomnographically verified sleep in 124 African American and Caucasian American women and men without a sleep disorder.

**Measurements and Results:** Circulating levels of 3 markers and/or mediators of inflammation known to be elevated in sleep disorders and in cardiovascular disease were determined (interleukin-6 [IL-6] endothelin-1 [ET-1], soluble intercellular adhesion molecule-1 [sICAM-1]). Sleep was characterized by polysomnography. Multiple linear regression analyses showed that increasing age, male sex, and African American ethnicity were independently associated with poorer sleep. After controlling for these variables, higher levels of ET-1 were independently associated with greater sleep latency (P ≤ 0.01), greater rapid eye movement (REM) latency (P ≤ 0.01), more slow wave sleep (P ≤ 0.05), and less stage 1 sleep (P ≤ 0.01). Higher IL-6 levels were independently associated with greater REM latency (P ≤ 0.05).

**Conclusions:** The findings suggest that, in individuals without a known sleep disorder, ET-1, a potent vasoconstrictor and mediator of inflammation, is associated with more deep sleep, whereas both ET-1 and IL-6 are associated with increased latency of sleep and of REM. The findings underscore the complex relationships between peripheral markers of inflammation and sleep.

**Keywords:** Inflammation, IL-6, ET-1, sICAM-1, sleep, coronary artery disease

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AN INFLAMMATORY STATE IS KNOWN TO EXIST IN SLEEP DISORDERS. INTERLEUKIN-6 (IL-6), FOR EXAMPLE, IS AN INFLAMMATORY CYTOKINE THAT IS elevated in sleep apnea and narcolepsy. Better sleep is associated with decreased daytime secretion of IL-6, whereas disturbed nocturnal sleep is associated with increased daytime IL-6 levels. Other markers of inflammation, including plasma endothelin-1 (ET-1) and the circulating soluble form of ICAM-1 (sICAM-1) may also be elevated in the setting of sleep disorders. ET-1 is a potent vasoconstrictor and mediator of inflammation elicited from endothelial cells. ICAM-1 is a ubiquitously expressed adhesion molecule important for leukocyte trafficking and basic inflammatory processes. In contrast to the literature on sleep and cytokines, such as IL-6 and IL-1ß, the linkages between elevated levels of ET-1 and sICAM-1 and disturbed sleep are less clear.

It is known that sleep disorders are associated with increased risk for coronary artery disease and that inflammation is a potential mechanism of this increased risk. The elevated circulating levels of IL-6 in obstructive sleep apnea are correlated with carotid intima-media thickness, suggesting that apnea-related systemic inflammation is associated with progression of atherosclerosis and increased risk of cardiovascular morbidity in these patients. The elevated sICAM-1 levels in patients with ischemic heart disease and sleep apnea increase their risk of atherosclerosis. Circulating ET-1 levels are likely elevated in obstructive sleep apnea and provide a link with increased risk for cardiovascular diseases.

Like sleep disorders, even sleep disturbances in the normal range have been associated with risk for coronary artery disease and might share similar inflammatory mechanisms. In healthy adults, a modest amount of sleep loss leads to an inflammatory response that could support basic cardiovascular diseases processes. Moderately elevated levels of IL-6 and sICAM-1 are associated with increased morbidity and mortality independent of other established risk factors.

The purpose of this study was to examine if the quality of sleep in relatively healthy individuals without a known sleep disorder is associated with inflammation. We assessed circulating levels of IL-6, sICAM-1, and ET-1 and a standard battery of polysomnography-derived indexes of sleep in a group of healthy men and women.

**METHODS**

**Participants**

Participants were recruited from the local community via advertisement and referrals. Recruitment efforts yielded a total of 385 individuals who expressed an interest in participating in the study. Of those, 151 employed (30+ hours/week) men and women between the ages of 23 and 54 years between 90% and 130% of their predicted ideal body weight completed the study. Participants who did not participate were ineligible due to not meeting the inclusion criteria, decided they were not interested, or could not be excused from work to participate. Participants with previously diagnosed sleep disorders, including sleep apnea, were excluded.
Women were excluded if postmenopausal, diagnosed with premenstrual syndrome, taking oral contraceptives, or pregnant. Individuals with psychiatric disorders or major medical conditions other than hypertension were also excluded from the study.

The study was approved by the University of California, San Diego Institutional Review Board. All subjects gave informed written consent.

Procedures

Participants completed a physical examination and answered questions about their medical history to determine eligibility for the study. Participants who met study entry criteria were then scheduled for 2 nights of sleep monitoring at the Gillin Laboratory of Sleep and Chronobiology at the University of California, San Diego, General Clinic Research Center. Participants arrived at the General Clinical Research Center at 17:00 on a weekday. During their first night, participants underwent an adaptation sleep study. Sleep set-up began at 20:00 and took approximately 1 hour. Lights were turned off at 22:00. After breakfast, participants left the General Clinical Research Center for the day, returning that evening at 20:00. During the second night at the General Clinical Research Center, an intravenous catheter was placed and a sleep recording was repeated with lights out at 22:00. Sleep data recorded during this second night were used for the study. Following this second night of sleep recording, a blood sample was taken via the catheter at 06:00 and before ambulation.

Demographics

Ethnicity was defined by subjects’ self-identification. Body mass index was computed as the ratio of body weight in kilograms divided by the square of height in meters (kg/m²). Resting blood pressure was computed as the average systolic and diastolic pressures based on 3 seated resting measurements. Given evidence that low socioeconomic status and African American ethnicity are associated with poorer sleep, we determined social class and identified the ethnicity of each subject. Social class was determined using the Hollingshead 2-factor index. African American and Caucasian American ethnicity were assessed via self-report. Because shift work adversely affects sleep quality, individuals engaged in shift work were excluded from the study. We studied normotensive and unmedicated hypertensive individuals (blood pressure > 140/90 mm Hg < 180/110 mm Hg).

Sleep Monitoring

Sleep data was recorded using standard polysomnography. Electroencephalography, electrooculography, chin electromyography, and thoracic and abdominal respiration were recorded on a Grass model PSG36-2 (Grass Heritage; West Warwick, RI). Oxyhemoglobin saturation was monitored using a pulse oximeter (Biox 3740, Ohmeda, Louisville, Colo) and analyzed by software from Profox (Escondido, Calif). Anterior tibialis electromyograms were used to rule out periodic limb movements during sleep. All records were scored with the Rechtschaffen and Kales criteria by technicians with interrater reliabilities above 90%.

We chose a panel of 8 sleep parameters that reflect the different domains of sleep and that prior studies suggest are or might reasonably be suspected to be related to our markers of inflammation. Percentage of sleep efficiency and sleep latency were chosen as objective indexes of sleep efficiency. Percentage of sleep efficiency was computed as the ratio of total sleep time to time spent in bed multiplied by 100. Arousal index was chosen to represent sleep fragmentation. An arousal was defined as a shift in electroencephalographic frequency to alpha or theta for at least 3 seconds but less than 15 seconds in duration, as scored from central, occipital, or both electroencephalogram leads. The total arousal index was defined by dividing the total number of arousals by the total sleep time. Percentage of sleep stages 1 and 2, percentage of slow wave sleep (SWS), percentage of rapid eye movement (REM) sleep, and REM latency were selected to describe sleep architecture. Sleep stages 3 and 4 were combined as SWS.

The number of apneas and hypopneas per hour of sleep were determined to obtain the apnea-hypopnea index. An apnea was defined as a decrement in airflow of at least 90% from baseline for at least 10 seconds. A hypopnea was defined as a decrement in airflow of 50% or greater but less than 90% from baseline for at least 10 seconds. The apnea-hypopnea index was defined as the number of apneas plus hypopneas per hour of sleep. Even though during the recruitment process we had excluded individuals with previously diagnosed sleep disorders, including sleep apnea, we identified 27 individuals with apnea-hypopnea indexes of more than 15. These individuals were excluded from the study, leaving a final sample size of 124 nonapneic subjects with a mean apnea-hypopnea index of 5.23 (SD= 4.1).

Biologic Assays

Whole blood was preserved with ethylenediaminetetraacetic acid. Obtained samples were spun in a refrigerated centrifuge and the plasma immediately frozen at -80°C until assay. sICAM-1, IL-6, and ET-1 were determined by commercial enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minn) using samples that had not been previously freeze-thawed. Intraassay coefficients of variation for sICAM-1, IL-6, and ET-1 were 3.95%, 2.3%, and 4.6%, respectively. The respective interassay coefficients of variation were 6.0%, 4.3%, and 5.5%.

Data Analysis

Pearson correlations were used to estimate bivariate relationships among the variables. One-way analyses of variance were used to test for differences according to sex and ethnicity. We used Fisher Least Significant Difference (LSD) Test to statistically adjust for simultaneous testing. We ran multivariate analyses of variance models (1 for each inflammatory marker) with a joint multivariate outcome defined by the 8 sleep variables. If the F-statistic from this model suggested a significant (P < 0.05) effect of inflammation on sleep, we then conducted individual multiple regressions assessing the association between the inflammatory marker and each sleep outcome. IL-6 and sICAM-1 were log transformed to obtain normal distribution. The statistical model assumptions were verified by graphing histograms and scatter plots to check that the outcome variables were Gaussian and that errors were homoscedastic. Data were analyzed using the SPSS 14.0 for Windows (SPSS Inc., Chicago, Ill) and presented as means (SD). The level of statistical significance was set at P
RESULTS

Subject Characteristics

Subject sociodemographic characteristics are presented in Table 1. Sleep and inflammatory marker characteristics are presented in Table 2 according to sex and ethnicity. Women had more efficient sleep ($F = 3.95, P < 0.049$), less stage 1 sleep ($F = 5.12, P < 0.025$), more SWS ($F = 6.68, P < 0.011$), longer sleep latency ($F = 5.55, P < 0.020$), and lower ET-1 levels ($F = 6.16, P < 0.014$). Caucasians had more efficient sleep ($F = 3.86, P < 0.050$), less stage 1 sleep ($F = 9.16, P < 0.003$) and stage 2 sleep ($F = 8.29, P < 0.005$), more SWS ($F = 25.5, P < 0.000$), less arousal ($F = 4.94, P < 0.028$), marginally shorter sleep latency ($F = 3.56, P = 0.061$), and lower IL-6 levels ($F = 3.91, P < 0.050$).

Bivariate Associations Between Subject Characteristics and Inflammation

IL-6 correlated with diastolic BP ($r = 0.220, P = 0.008$) and age ($r = 0.226, P = 0.013$). sICAM-1 correlated with systolic blood pressure ($r = 0.227, P = 0.007$), age ($r = -0.201, P = 0.014$) and social class (higher levels in lower social class) ($r = 0.233, P = 0.005$). ET-1 correlated with systolic blood pressure ($r = 0.169, P = 0.041$) and social class (higher levels in lower social class) ($r = 0.236, P = 0.004$).

Bivariate Associations Between Sleep and Inflammation

IL-6 correlated with sleep efficiency ($r = -0.279, P = 0.001$), percentage of stage 1 sleep ($r = 0.184, P = 0.030$), and marginally with percentage of SWS ($r = -0.156, P = 0.068$) and arousal index ($r = 0.158, P = 0.069$). ET-1 correlated with REM latency ($r = 0.227, P = 0.007$) and sleep latency ($r = 0.247, P = 0.003$).

MANOVA Findings

The multivariate tests that included all 8 sleep variables were significant for IL-6 ($F = 2.45$, Wilk’s Lambda $P$ value = 0.017) and ET-1 ($F = 2.40$, Wilk’s Lambda $P$ value = 0.019). The sICAM-1 multivariate analysis of variance was not significant ($F = 1.56$, Wilk’s Lambda $P$ value = 0.330). Based on this analysis and Fisher LSD test, we fitted separate multiple linear regression models assessing the association between each sleep measure and IL-6 and ET-1.

Table 1—Sociodemographic Characteristics of the 124 Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>38.6 (6.8)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.5 (5.7)</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>124.6 (13.5)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>74.9 (10)</td>
</tr>
<tr>
<td>Hypertensive</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21</td>
</tr>
<tr>
<td>No</td>
<td>103</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>65</td>
</tr>
<tr>
<td>Men</td>
<td>59</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>58</td>
</tr>
<tr>
<td>Caucasian-American</td>
<td>68</td>
</tr>
<tr>
<td>Social Class</td>
<td>3.07 (1.01)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) or number.

Table 2—Inflammatory Markers and Sleep

<table>
<thead>
<tr>
<th>Inflammatory markers</th>
<th>Women</th>
<th>Men</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6, pg/mL</td>
<td>1.58 (1.85)</td>
<td>1.67 (1.65)</td>
<td>1.93 (2.23)</td>
</tr>
<tr>
<td>sICAM-1, ng/mL</td>
<td>206.0 (73.2)</td>
<td>223.0 (81.9)</td>
<td>205.0 (90.7)</td>
</tr>
<tr>
<td>ET-1, pg/mL</td>
<td>2.68 (0.86)</td>
<td>3.05 (0.94)</td>
<td>2.85 (0.86)</td>
</tr>
<tr>
<td>Sleep parameter</td>
<td></td>
<td></td>
<td>2.89 (0.97)</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>90.7 (0.82)</td>
<td>87.8 (0.88)</td>
<td>87.7 (0.85)</td>
</tr>
<tr>
<td>Latency, min</td>
<td>14.6 (18)</td>
<td>8.67 (12)</td>
<td>14.2 (18)</td>
</tr>
<tr>
<td></td>
<td>91.8 (45)</td>
<td>80.3 (36)</td>
<td>84.0 (45)</td>
</tr>
<tr>
<td>Arousal index, no/h</td>
<td>6.45 (4.7)</td>
<td>7.39 (5.2)</td>
<td>7.92 (4.5)</td>
</tr>
<tr>
<td>Sleep stage, %</td>
<td></td>
<td></td>
<td>6.06 (5.2)</td>
</tr>
<tr>
<td>1</td>
<td>6.03 (3.7)</td>
<td>7.57 (4.4)</td>
<td>7.93 (4.8)</td>
</tr>
<tr>
<td>2</td>
<td>63.0 (8.6)</td>
<td>64.6 (8.2)</td>
<td>65.9 (7.6)</td>
</tr>
<tr>
<td>SWS</td>
<td>9.89 (8.2)</td>
<td>6.49 (8.2)</td>
<td>62.0 (8.7)</td>
</tr>
<tr>
<td>REM sleep, %</td>
<td>20.9 (6.1)</td>
<td>21.3 (5.9)</td>
<td>21.4 (6.4)</td>
</tr>
</tbody>
</table>

IL-6 refers to interleukin-6; sICAM-1, soluble intercellular adhesion molecule-1; ET-1, endothelin-1; REM, rapid eye movement sleep

* > in African-Americans, $P < 0.05$

* > in men, $P < 0.05$

* > in women and Caucasian Americans, $P < 0.05$

* > in women and African Americans, $P < 0.05$

* > in men and African-Americans, $P < 0.05$
Multivariate Associations Among Sleep, Inflammation, and Subject Characteristics

The individual multiple linear regression analyses were aimed at determining the extent to which inflammatory variables predicted sleep variables independently of demographic variables. Hence, sets of variable were entered in blocks. Age, sex (0 = male, 1 = female), ethnicity (0 = Caucasian American, 1 = African American), and social class were entered in the first block. Given the effects of hypertension and obesity on inflammation, systolic blood pressure, diastolic blood pressure, and body mass index were entered in the second block. The apnea-hypopnea index was entered in the third block. IL-6 and ET-1 were entered in the fourth block.

Results of the regression analyses for each sleep variable are presented in Table 3. Demographic factors of age and sex were consistently associated with attributes of sleep, while ethnicity and body mass index were less consistently associated with sleep. In general, increasing age, male sex, African American ethnicity, and increasing body weight were associated with poorer sleep.

Inflammatory markers were predictive of 4 of the 8 sleep indexes with higher levels of ET-1 and/or IL-6 being associated with greater sleep latency and REM latency and less stage 1 but more SWS sleep (Table 3).

Less efficient sleep (percentage sleep efficiency) was predicted by older age (model adjusted R² = 0.103, P < 0.006). Greater arousal (arousal index) was predicted by older age (model adjusted R² = 0.161, P ≤ 0.002).

Longer sleep latency was predicted by younger age, being female, being African American, having higher diastolic blood pressure (marginal effect), and higher levels of ET-1 (model adjusted R² = 0.156, P ≤ 0.001). Longer REM latency was predicted by being female and having higher ET-1 and IL-6 levels (model adjusted R² = 0.116, P ≤ 0.005).

Less SWS was predicted by older age, being male, being African American, having higher body mass index, having lower systolic blood pressure, and lower levels of ET-1 (model adjusted R² = 0.379, P ≤ 0.001). Percentage of stage 1 sleep was predicted by age (more in older subjects), sex (marginal effect, more in men), body mass index (more in heavier subjects) and lower ET-1 levels (model adjusted R² = 0.201, P ≤ 0.001). Percentage of stage 2 sleep was predicted by age (more in older subjects) (model adjusted R² = 0.151, P ≤ 0.001). Percentage of REM sleep too was predicted by age (less in older subjects) (model adjusted R² = 0.031, P ≤ 0.044).

DISCUSSION

This study sought to determine whether inflammatory markers known to be elevated in individuals with sleep disorders are related to sleep in individuals without a known sleep disorder. We selected a panel of inflammatory markers known to be elevated in disorders of sleep and with known linkages to coronary artery disease. We attempted to control for a number of factors known to affect sleep quality. We tested for and excluded individuals with obstructive sleep apnea syndrome. In addition, we identified and controlled for a number of other potential confounding factors known to affect sleep, including age, sex, ethnicity, and social class. Because antihypertensive medications might affect some characteristics of sleep, we studied only individuals who were not taking antihypertensive medication. To ensure as much standardization as possible of sleep recordings and the sleep environment, the study was conducted in the controlled setting of a General Clinical Research Center using standard polysomnography following an acclimatization night.

Across all of the predictor variables we examined, age and sex were most consistently related to sleep, with older age and male sex generally predicting poorer sleep. Age-related changes in sleep are believed to be due to weaker circadian regulation of sleep and wakefulness. Findings on effects of sex on sleep in healthy populations are not consistent. Race has previously been demonstrated to be a predictor of sleep quality, with studies suggesting that African Americans have poorer sleep than Caucasian Americans. When controlling for other variables, we found that African Americans had longer sleep latencies, more stage 1 and stage 2 sleep, and less SWS. Higher blood pressure was marginally associated with prolonged sleep latency and more SWS. Consistent with the sleep literature, a heavier body mass index was associated with more stage 1 sleep and less SWS.

Independent of these effects of demographic factors, higher circulating levels of ET-1 and/or IL-6 were associated with greater sleep latency and REM latency, less stage 1 sleep, and more SWS.

Table 3—Multiple Regression Predictors of Sleep

<table>
<thead>
<tr>
<th>Sleep variable</th>
<th>Significant individual predictor variables (ß coefficients; P values)</th>
<th>Model unadjusted R²; adjusted R²; P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep efficiency</td>
<td>Age (-0.003; 0.004)</td>
<td>0.139; 0.103; P = 0.006</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>Age (-0.543; 0.026); sex (6.83; 0.045); ethnicity (6.68; 0.059); diastolic BP (0.309; 0.075); ET-1 (5.41; 0.003)</td>
<td>0.208; 0.156; P = 0.001</td>
</tr>
<tr>
<td>Arousal index</td>
<td>Age (0.272; 0.000)</td>
<td>0.223; 0.161; P = 0.002</td>
</tr>
<tr>
<td>Stage 1 sleep</td>
<td>Age (0.183; 0.002); sex (-1.39; 0.085); BMI (0.165; 0.014); ET-1 (-3.317; 0.005)</td>
<td>0.242; 0.201; P = 0.000</td>
</tr>
<tr>
<td>Stage 2 sleep</td>
<td>Age (0.404; 0.000)</td>
<td>0.176; 0.151; P = 0.000</td>
</tr>
<tr>
<td>SWS</td>
<td>Age (-0.442; 0.000); sex (3.87; 0.005); ethnicity (-3.882; 0.008); BMI (-0.325; 0.004); systolic BP (0.996; 0.036); ET-1 (1.33; 0.050)</td>
<td>0.423; 0.379; P = 0.000</td>
</tr>
<tr>
<td>REM latency</td>
<td>Sex (17.4; 0.033); ET-1 (33.3; 0.004); IL-6 (12.2; 0.023)</td>
<td>0.161; 0.116; P = 0.005</td>
</tr>
<tr>
<td>REM percentage</td>
<td>Age (-0.164; 0.044)</td>
<td>0.042; 0.031; P = 0.044</td>
</tr>
</tbody>
</table>

* ∆R² indicates additional variance accounted for by inflammatory marker where applicable

BP refers to blood pressure; ET-1, endothelin-1; BMI, body mass index; SWS, slow wave sleep; IL-6 = interleukin-6; REM, rapid eye movement; sex (0 = male, 1 = female); ethnicity (0 = Caucasian American, 1 = African American)
Our IL-6 findings are consistent with prior studies indicating a relationship between circulating levels of IL-6 and sleep quality. Work by Vgontzas et al indicates that IL-6 is a mediator of sleepiness, its circadian pattern reflecting the homeostatic drive for sleep. IL-6 is secreted in a biphasic circadian pattern with 2 zeniths at about 05:00 and 19:00 and 2 nadirs at about 08:00 and 21:00. In this study, blood was collected at 06:00, which is between the zenith of 05:00 and the nadir of 08:00. IL-6 levels drawn at 06:00 were found to independently and positively correlate with REM latency. Prior work by Motivala et al reports that IL-6 levels sampled at 13:00 are independently related to greater REM density in major depression. In this study, even when IL-6 was assumed to have reached its nadir in the early morning, it showed a significant relation to REM latency, suggesting that even comparatively low levels of IL-6 might be associated with sleep quality, highlighting the potential role of this cytokine for sleep medicine research.

Interestingly, ET-1 showed significant independent relationships with 4 of the 8 sleep variables examined. We found that, independent of blood pressure, higher levels of ET-1 were related to less time in stage 1 sleep and more time in SWS. In contrast with more clear mechanistic linkages in the literature between sleep and the somnogenic cytokine IL-6, possible linkages between sleep and inflammatory factors such as ET-1 are yet to be elucidated. The majority of studies that have examined ET-1 and sleep have been conducted in patients with sleep apnea, with a particular interest in seeking to understand the relationship between apnea and elevated blood pressure. In healthy individuals, circulating ET-1 levels show significant variations during the sleep cycle, paralleling changes in blood pressure. Similarly, in patients with sleep apnea, ET-1 is strongly related to hypertension, with blood pressure correlating positively with circulating ET-1 levels. ET-1 levels are also increased with sleep deprivation and can be successfully lowered in patient with sleep apnea treated with continuous positive airway pressure. The elevated ET-1 in sleep apnea appears to be related to the oxyhemoglobin desaturation. Such findings suggest that ET-1 is more a consequence than a determinant of sleep quality. Sleep apnea is also characterized by repetitive sympathetic bursts during hypoxia. Accordingly, increased ET-1 has also been observed in response to sympathomedullary activation in healthy subjects. Unfortunately, our study design did not allow us to investigate a pathway leading from a longer sleep latency, longer REM latency, and more SWS to sympathomedullary activation and ET-1 release further downstream.

How do the circulating levels of the inflammatory markers we examined in this healthy population compare with clinical conditions? ET-1 levels in established hypertension and after acute myocardial infarction are in the range of 1 to 4.5 pg/mL, which is similar to that of our subjects. In contrast, IL-6 levels in our healthy subjects were substantially lower than those seen in acute coronary syndromes, which can exceed 100 pg/mL. The sICAM-1 levels in our subjects were lower than are levels typically seen in patients after stroke and acute coronary syndrome (244-340 ng/mL). However, it is important to distinguish between levels of inflammatory markers during acute cardiovascular events and the predictive value of subtle steady-state elevations in the normal range of healthier populations. From a clinical perspective, it has been shown that perceived troubles with falling asleep are associated with risk of coronary artery disease, and difficulties initiating sleep have also been shown to predict mortality from coronary artery disease in middle-aged men at several-year follow-up. Our finding of increased ET-1 with greater sleep latency concurs with this literature, suggesting that the longer it took subjects to fall asleep, the higher were their ET-1 levels and potentially associated cardiovascular risk. In contrast with prolonged sleep latency, amounts of stage 1 sleep, SWS, and REM latency have, to the best of our knowledge, not previously been associated with cardiovascular risk. Theoretically, more SWS along with less stage 1 sleep together suggest deeper sleep, which is assumed to have health benefits. However, we feel it is premature to interpret the direction of the association between our sleep architecture measures and ET-1 and IL-6 in terms of cardiovascular risk.

There are several limitations to this study that should be addressed. We examined a panel of 3 inflammatory markers with known relevance to disturbed sleep and cardiovascular disease risk, but there are many other such markers, including IL-1β, IL-18, and tumor necrosis factor-α that merit examination in this context. Our assessment of inflammation was based on a single blood sample. Clearly, a more ideal design, particularly for IL-6, which exhibits a circadian rhythm, would be multiple sampling times. We did not exclude individuals with mild hypertension but did control for blood pressure in each regression analysis. Despite these limitations, the findings provide insight into possible associations between sleep and markers of inflammation in a sample of healthy individuals.

In summary, the findings suggest that, in individuals without a known sleep disorder, ET-1 is associated with more deep sleep, whereas ET-1 and IL-6 are associated with increased latency of sleep and of REM. The relationship between peripheral markers of inflammation and sleep in relatively healthy individuals appears less straightforward than in individuals with disrupted sleep or sleep disorders.

ACKNOWLEDGMENTS

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