

Association Between Nocturnal Vagal Tone and Sleep Depth, Sleep Quality, and Fatigue in Alcohol Dependence

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Background: This study examined whether nocturnal vagal tone as indexed by the high-frequency (HF) power component of heart rate variability is related to measures of sleep depth and daytime perceptions of sleep quality, sleepiness, and fatigue in alcohol dependence. **Methods:** Abstinent alcohol-dependent patients ($n = 14$) and comparison control subjects ($n = 14$) underwent all-night polysomnography along with assessment of heart rate variability during an awake period before sleep and during sleep. Sleep-quality perceptions, along with self-reported sleepiness and levels of energy and fatigue, were obtained in the morning. **Results:** As compared with control subjects, alcohol-dependent persons showed marked decreases in delta sleep along with impairments of sleep quality and daytime energy. In addition, alcoholics showed a decrease of the HF power component of heart rate variability during the awake period before sleep and during nocturnal sleep as compared with control subjects. HF power during the awake period before sleep correlated with electroencephalographic delta sleep and delta power observed during the subsequent sleep period. HF power during the awake period before sleep also correlated with morning reports of sleep quality, sleepiness, and fatigue. **Conclusions:** Alcohol dependence compromises vagal output measured before sleep onset, which correlates with loss of delta sleep and with morning reports of sleep impairments. Testing of interventions that target sympathovagal balance might identify new strategies for partial amelioration of the sleep disturbances and impairments in daytime functioning observed in persons with alcohol dependence. **Key words:** alcoholism, sleep, fatigue, sympathetic nervous system, parasympathetic nervous system, heart rate variability, vagal tone.

ANOVA = analysis of variance; BMI = body mass index; DSM-IV = Diagnostic and Statistical Manual-IV; EKG = electrocardiogram; EEG = electroencephalogram; EMG = electromyography; EOG = electrooculography; h = hours; HF = high frequency; Hz = hertz; LF = low frequency; NREM = nonrapid eye movement; POMS = Profile of Mood States; PSG = polysomnography; PSQI = Pittsburgh Sleep Quality Index; REM = rapid eye movement.

INTRODUCTION

In the general population, lifetime prevalence of alcohol dependence exceeds 10% (1). Insomnia, one of the most common symptoms reported in recovering alcoholics, is associated with significant impairments in daytime functioning, sleepiness, and fatigue (2–4). In turn, recovering alcoholics who report insomnia are at increased risk for relapse and a return to heavy drinking (5–8). Electroencephalogram (EEG) sleep studies further show disturbances in sleep initiation along with a profound loss of delta sleep and delta power as measured by spectral analyses in abstinent alcohol-dependent patients (9–12). Furthermore, impairments in the ability to generate delta sleep are found in which alcohol-dependent persons fail to show an augmentation of delta sleep after sleep loss, suggesting a defect in the processes that regulate delta sleep accumulation (9).

The neurobiologic mechanisms that underlie abnormal regulation of delta sleep in alcoholics remain largely unknown, although multiple factors have been implicated, including

direct neural toxicity (13), a delay in the nocturnal release of melatonin (14), and increases in proinflammatory cytokine activity in recovering alcoholics (15). Emerging evidence also suggests that alcohol dependence affects sympathovagal balance as measured by heart rate variability (16,17), a noninvasive method for assessing cardiac autonomic tone, which estimates sympathetic and parasympathetic nervous system activity (18) and links changes in autonomic function to underlying central nervous system activity, including EEG sleep (19,20).

Assessment of heart rate variability involves spectral analytic techniques to identify a high-frequency power component (HF; 0.15–0.4 Hz) that is mediated by parasympathetic activity and a low-frequency power component (LF: 0.04–0.15 Hz) that is related to a combination of sympathetic and parasympathetic effects (18). The ratio of LF/HF refers to the degree of sympathovagal balance and has been used to infer relative sympathetic nervous system activity (18). As compared with wakefulness, nonrapid eye movement (NREM) sleep is associated with an increase of HF power with further progressive increases in this frequency component during delta sleep (21,22). Indeed, modeling of the reciprocal relationships between sympathovagal balance and EEG sleep suggest common control mechanisms in which delta activity emerges as sympathovagal balance decreases or as power in the HF component increases (23,24).

Less is known about nocturnal sympathovagal balance in patients with disordered sleep. One study found that patients with chronic insomnia show nocturnal sympathetic hyperactivity as evidenced by increases of power in the LF component (25), consistent with elevated nocturnal levels of circulating catecholamines (26). It is hypothesized that heightened activation and a shift toward sympathetic dominance contributes to decreases of sleep maintenance and depth, although data are limited (25,27). To our knowledge, no studies have examined whether abnormalities of nocturnal sympathovagal balance are related to reports of sleep quality and daytime measures of

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Received for publication May 24, 2005; revision received September 22, 2005.

This work was supported in part by grants AA13239, DA16541, MH55253, AG18367, T32-MH19925, M01-RR00865, and M01 RR00827, General Clinical Research Centers Program, and the Cousins Center for Psychoneuroimmunology.

DOI: 10.1097/01.psy.0000195743.60952.00

sleepiness and fatigue, which are critical symptoms of insomnia in alcohol dependence.

This study evaluated heart rate variability and EEG sleep along with reports of sleep quality and daytime levels of sleepiness and energy in abstinent alcohol-dependent subjects as compared with age-, gender-, and ethnicity-matched control subjects. Two hypotheses regarding the autonomic mechanisms that underlie abnormal sleep and sleep impairments in alcohol dependence were examined. The first hypothesis posited that alcoholics would show abnormalities of delta sleep, sleep quality, and daytime impairments, and that decreases of the HF component of heart rate variability would also be found during sleep in these patients. The second hypothesis concerned autonomic modulation of sleep depth and sleep quality; this hypothesis proposed that levels of the HF component before sleep would also be associated with loss of delta sleep, impairments in perceived sleep quality, and daytime reports of sleepiness and fatigue in alcohol dependence.

METHODS AND MATERIALS

Research Participants

All study procedures were approved by the UCLA Institutional Review Board. Alcohol-dependent patients, recruited by flyers and by referral from UCLA-affiliated alcohol treatment programs, fulfilled Diagnostic and Statistical Manual-IV (DSM-IV) criteria for alcohol dependence that had occurred in the absence of major preexisting or concomitant psychiatric disorders (28), including secondary depression (29). Control subjects, recruited by advertisements, fulfilled DSM-IV criteria for never mentally ill (28) and were matched to alcohol-dependent subjects on the basis of age (± 5 years), gender, ethnicity, income or employment status, and body mass index (BMI ± 3 weight in kilograms/height in square meters) because each of these variables is associated with heart rate variability (18). None of the subjects were obese: all BMIs < 30 kg/m².

A total of 32 men fulfilled screening eligibility criteria, gave informed consent, and entered the research protocol. Of this total, four alcohol-dependent subjects were excluded as a result of reports of alcohol consumption and/or positive toxin screens during the sleep protocol or within the 2-week period before assessment. Hence, four control subjects who were matched to the alcohol-dependent patients were also excluded from the study. The remaining sample was comprised of 28 men (14 control subjects, 14 alcoholic patients). All participants were free of major medical illnesses as determined by medical history and laboratory screening blood tests. None of the subjects fulfilled criteria for primary substance dependence or had used substances in the last 2 weeks; had currently treated hypertension or overt alcohol-related liver disease; showed elevations of liver function tests above the laboratory range of normal; or were taking medications known to alter sleep wake activity (e.g., β -blockers, psychotropic medications) within 2 weeks of the sleep protocol. Alcoholics were studied after acute and subacute withdrawal symptoms had resolved; all subjects reported an abstinence period of greater than 14 days before admission to the sleep protocol. Random urine substance screens were used to confirm abstinence in the 2 weeks before and during the sleep protocol.

Procedures

Research diagnoses of control and alcoholic patients were made following the administration of a semistructured interview developed by the multisite Collaborative Study on the Genetics of Alcoholism (30), which also provided interview data on alcohol and other substance, including tobacco, consumption histories. Details about the sleep screening, sleep protocol, and EEG sleep methods have been previously described (9,10). Two weeks before entry into the study, sleep-wake activity diaries were obtained in alcoholics and control subjects. All subjects were sleeping regularly between 10:00 PM and 7:00 AM. The sleep protocol, performed in the UCLA General Clinical Research Center

(GCRC), was preceded by 1 night of adaptation with screening for sleep apnea and nocturnal myoclonus. The study protocol involved a night of uninterrupted baseline sleep in which subjects were at supine rest from 10:00 PM to 7:00 AM with lights out at 11:00 PM. During the nocturnal period, a bedside urinal was used if subjects needed to urinate during the night. Subjects remained on the GCRC during the day with hourly nursing observation to ensure abstinence over the course of the sleep protocol; current smokers were asked to stop smoking for 4 hours before the sleep assessment to control for nicotine's influence on sympathovagal activity. In addition, subjects were asked to refrain from physical exertion, and during the nocturnal period, none were allowed to eat or to smoke. Awakening of subjects occurred in the morning by turning on a dim light and calling the subject's name.

The polysomnography (PSG) montage included four EEG channels (C₃, C₄, O₁, O₂) referenced to A₁-A₂, bilateral electrooculography (EOG), bipolar submental electromyography (EMG), pulse oximetry, abdominal respiratory effort, and electrocardiogram (EKG). PSG measures were obtained during continuous recordings between 11:00 PM and 7:00 AM. Sleep records were visually scored as previously described (9,10). Data from each 30-second epoch were entered into a computer program that tallies the summary statistics for each subject. To quantify EEG frequency characteristics, the sleep EEG, from sleep onset to good morning time, was digitized (128 Hz) and power spectra for 4-second epochs were then determined for a 0.25- to 64.0-Hz range. The transformed data were then further compressed into six frequency bands (0.75-4.5 Hz δ , 4.5-7.5 Hz θ , 7.5-11 Hz α , 11-12.25 Hz [slow spindle frequencies], 12.25-16 Hz [fast spindle frequencies], 16-40 Hz β), and mean power density ($\mu\text{V}^2/\text{octave}$) and peak frequency (Hz) were calculated for each band as previously described (10,31,32). These frequency bands are characteristic of certain sleep stages. For instance, the delta frequency band (0.75-4.50 Hz) is characteristic of stage 3 and 4 sleep (slow-wave sleep), the theta (4.50-7.50 Hz) and spindle (slow spindle: 11.00-12.25 Hz, fast spindle: 12.25-16.00 Hz) frequency bands are characteristic of stage 2 sleep, and both the alpha and beta frequency bands (7.5-11 Hz; 16.00-40.00 Hz) are characteristic of wakefulness and/or arousability. Furthermore, delta and beta bands are indicative of sleep depth. Five-minute epochs were used to determine the power in each frequency band after good nighttime for the first NREM, second NREM, and third NREM periods, and for the first REM, second REM, and third REM periods.

At 8:00 PM and 8:00 AM before and after the sleep protocol, behavioral states of sleepiness, activation, and fatigue were evaluated by administration of the Stanford Sleepiness Scale (33) and the Profile of Mood States "vigor" and "fatigue" items (34,35). The Pittsburgh Sleep Quality Index (PSQI) was used to assess perceived sleep quality and to screen for clinical sleep impairment as defined by PSQI scores > 5 (36).

The subject's EKG signal was sampled at a frequency rate of 200 Hz, and an interpolation algorithm was used to optimize temporal accuracy of R wave peak detection (37). The signal was then converted into an RR interval signal and spectral analyzed using a 12-point autoregressive algorithm (Somnologica, Flaga hf, Medical Devices, Iceland) in accordance with recommended guidelines to generate estimates of high and low frequency (18). Across the entire nocturnal period, the EKG signal was analyzed using 5-minute segments; each used segment was free of EKG artifacts and EEG arousals at least 30 seconds before and during the recording period. Hence, after visual inspection of each epoch by a rater blind to group status, epochs were included if the following criteria were fulfilled: same stage of sleep across the 5-minute segment; no EEG arousals during or 30 seconds before the epoch; no evidence of EKG artifacts such as movement, poor contact, or 60-cycle artifacts; and no EKG arrhythmias. Heart rate variability assessment during the awake period, before sleep onset, was obtained with subjects' eyes closed with 10 minutes of recording beginning at 10:30 PM, before "lights out" at 11:00 PM. Throughout this recording of heart rate variability during the awake period, subjects were directed to "rest quietly;" measures were taken while subjects were at supine rest in bed. For heart rate variability, two spectral variability measures were examined: low-frequency power defined as the total spectral power in the 0.04- to 0.15-Hz frequency band (LF) and high-frequency power defined as the total spectral power in 0.15- to 0.4-Hz

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frequency band (HF). The LF/HF ratio was calculated by dividing the LF power component by the HF power component.

For analyses of heart rate variability during sleep stages, 5-minute segments were averaged during the waking period before sleep, stage 2 sleep, and REM sleep. EKG signals were not analyzed during delta sleep because the alcohol-dependent subjects had little to no delta sleep amounts. For analyses of heart rate variability during each successive period of NREM and REM sleep, 5-minute segments were averaged during each of those periods. For all scoring of EEG sleep and heart rate variability data, the rater(s) were blind to group assignment.

Statistical Analyses

Data were analyzed using SPSS version 11.5 for Windows and missing values were substituted by single-point multiple imputation using NORM version 2.03 for any participant who had more than 95% of their data. Group differences on clinical variables and measures of EEG sleep were tested using paired *t* tests given the matched-pair experimental design. To determine main effects of group (alcohol dependence versus control), sleep stage (awake before sleep, stage 2, REM sleep), and their interaction on heart rate variability assessments, repeated-measures analyses of variance (ANOVA) was used. Likewise, repeated-measures ANOVAs were used to evaluate main effects of group, successive periods of NREM sleep or of REM sleep, and their interaction on heart rate variability measures. Age, ethnicity, income, BMI, and physical activity were not covaried because the two groups were comparable on these clinical confounders (Table 1). Nonparametric Spearman correlations were used to evaluate relationships among heart rate variability assessment periods and delta sleep. These correlational analyses were restricted to delta sleep measures given the a priori hypotheses and group differences in this measure of EEG sleep. Three heart rate variability assessment periods (awake before sleep onset, stage 2, and REM) were tested in relation with delta sleep measures (amount and percentage of delta sleep; delta power). Exploratory analyses between number of awakenings and heart rate variability assessments were also conducted given prior evidence linking insomnia and increases in LF power (25). Finally, nonparametric Spearman correlations were used to test the relationships between heart rate variability assessment periods and reports of sleep quality, sleepiness, and fatigue.

RESULTS

Sample

Alcohol-dependent subjects were not significantly different from control subjects on the demographic and clinical variables, including age, ethnicity, employment status, income, BMI, and average weekly physical activity (Table 1). As expected, alcoholics reported greater and more recent consumption of alcohol and were more likely to be tobacco smokers than control subjects.

Sleep Encephalography

Table 2 shows the group differences in EEG sleep. Consistent with our prior findings in a different sample (9,10), alcohol-dependent persons had more stage 1 sleep and less stage 3 sleep, stage 4 sleep, and delta sleep as compared with control subjects. No group differences were found for measures of sleep continuity or REM measures. For EEG spectral analyses, alcoholics showed decreases of power in delta, theta, spindle, and beta frequencies during both the first NREM and REM periods as compared with control subjects (Table 3). Similar results were found during the second and third NREM and REM periods, although group differences during these periods did not reach statistical significance except for delta activity during the second and third NREM periods.

Reports of Sleep Impairments

Evaluation of sleep quality as measured by the PSQI showed that alcohol-dependent patients had higher mean scores (8.8 ± 4.0) than the control subjects (3.8 ± 2.8 ; $t = 3.7$, $p < .001$). In addition, 71% of the alcoholics were rated as having clinically significant sleep impairments with PSQI

TABLE 1. Age, Ethnicity, Income, Body Mass Index, Physical Activity, and Alcohol and Tobacco Consumption Histories in Control and Alcohol-Dependent Groups

Variables	Control (<i>n</i> = 14)		Alcohol Dependent (<i>n</i> = 14)		Alcoholism Effect	
	Mean	SD	Mean	SD	<i>t</i>	<i>p</i>
Age (yrs)	37.5	9.8	39.1	6.4	0.5	.6
Income (\$10,000)	3.6	2.2	2.9	2.0	1.0	.34
Body mass index ^a	24.3	3.5	26.1	2.3	1.6	.12
Physical activity (kcal/day)	3179.2	720.5	3925.8	1565.7	1.6	.12
Alcohol consumption (last 3 months)						
Drinking days/month	5.9	17.1	24.9	5.9	3.9	.001
Drinks/day	0.9	1.2	10.7	8.4	4.3	.001
Days since last drink	119.6	139.0	31.0	28.0	2.3	.03
Alcohol dependence (no. of withdrawal symptoms)	NA		15.1	7.5		
Age onset of dependence	NA		26.9	5.7		
	<i>n</i>	Percent	<i>n</i>	Percent	χ^2	<i>p</i>
Ethnicity: black	5	36	5	36	2.3	.33
Employment: working	5	36	7	50	1.3	.43
Tobacco smokers	2	14	8	57	6.5	.02

^a Weight in kilograms/height in square meters.
SD = standard deviation.

TABLE 2. Sleep Continuity, Sleep Architecture, and Rapid Eye Movement (REM) Sleep Measures in Alcohol-Dependent and Control Groups

EEG Sleep Variables	Control (<i>n</i> = 14)		Alcohol Dependent (<i>n</i> = 14)		Alcoholism Effect	
	Mean	SD	Mean	SD	<i>t</i>	<i>p</i>
Sleep continuity						
Total sleep time (min)	388.8	74.5	372.4	79.9	0.51	.62
Sleep onset (min)	20.4	15.0	28.2	48.5	-0.56	.59
Sleep efficiency	78.0	15.0	81.0	12.4	-0.56	.58
Sleep architecture						
Stage 1 (%)	5.9	2.2	8.8	3.9	-2.21	.05
Stage 2 (%)	65.6	8.6	63.6	18.9	0.36	.72
Stage 3 (%)	6.6	4.1	1.4	2.6	4.3	.001
Stage 4 (%)	1.8	3.8	0.7	2.7	2.6	.02
Delta (%)	8.4	6.3	2.1	5.1	2.9	.007
REM (%)	20.2	8.2	21.4	8.5	0.5	.19
REM measures						
REM latency, corrected	60.3	29.7	48.3	32.7	1.4	.18
REM duration (First period)	13.2	11.0	18.3	9.7	-1.3	.23
REM density	1.9	0.8	2.4	0.5	-1.8	.09

EEG = electroencephalogram; SD = standard deviation.

TABLE 3. Electroencephalogram (EEG) Spectral Analyses During the First Period of nonrapid Eye Movement (REM) and REM Sleep in Alcohol-Dependent and Control Groups

Spectral EEG Sleep Variables	Control (<i>n</i> = 14)		Alcohol Dependent (<i>n</i> = 14)		Alcoholism Effect	
	Mean	SD	Mean	SD	<i>t</i>	<i>p</i>
Non-REM first period						
Delta activity (0.75–4.50 Hz)	86.2	61.5	51.9	56.4	2.6	.03
Theta (4.50–7.50 Hz)	34.2	22.6	20.7	13.6	2.4	.04
Spindle power (12.25–16.00 Hz)	19.5	10.2	12.6	8.7	2.0	.06
Beta (16.0–40.00 Hz)	3.3	1.3	2.4	0.9	3.2	.008
REM first period						
Delta (0.75–4.50 Hz)	17.7	9.9	10.6	8.7	2.9	.02
Theta (4.50–7.50 Hz)	21.7	15.3	13.3	11.9	2.6	.03
Spindle (12.25–16.00 Hz)	8.2	5.4	5.8	3.5	1.4	.18
Beta (16.0–40.00 Hz)	4.1	2.6	2.8	1.2	1.9	.09

scores >5 as compared with only 14% of the controls ($\chi^2 = 9.9, p < .005$). Ratings of behavioral symptoms of sleepiness, vigor, and fatigue showed similar results for measures taken at 8:00 PM and 8:00 AM. As compared with control subjects, alcoholics showed increases of Stanford sleepiness ($t = 1.7, p = .06; t = 1.7, p = .06$) and decreases of Profile of Mood States (POMS) vigor ($t = 2.2, p < .05; t = 2.1, p < .05$) at the 8:00 PM and 8:00 AM time points, respectively. No group differences in measures of POMS fatigue were found at either time point.

Heart Rate Variability

For heart rate, a repeated-measures ANOVA across three sleep stages (i.e., waking before sleep, stage 2 sleep, and REM sleep) showed a significant group effect with alcoholics having higher heart rates as compared with control subjects ($F [1, 24] = 8.9, p < .01$). There was a significant effect for sleep stage ($F [2, 52] = 15.6, p < .01$) but no group-by-sleep-stage interaction. Similarly, across three successive periods of

NREM or REM sleep, alcoholics showed higher heart rates both for NREM and for REM successive periods as compared with control subjects (group effect: $F [1, 24] = 7.2, p < .05; F [2, 52] = 5.5, p < .05$). There were also significant period effects both for NREM sleep and for REM sleep with increases across the night ($F [2, 52] = 7.2, p < .01; F [2, 52] = 12.2, p < .001$) but no interactions (data not shown).

For spectral analyses of heart rate variability HF power (0.15–0.4 Hz, ms^2), repeated-measures ANOVA across three sleep stages (i.e., waking before sleep, stage 2 sleep, and REM sleep) showed a significant group effect with alcoholics having lower levels of HF power as compared with control subjects ($F [1, 24] = 5.0, p < .05$). There was a significant effect for sleep stage ($F [2, 52] = 7.8, p < .001$) but no group-by-sleep-stage interaction (Fig. 1). For the three successive periods of NREM and REM sleep, no significant main effects for group, NREM/REM period, or interactions were found. However, given group differences for HF across the three sleep stages as well as prior reports of a differential

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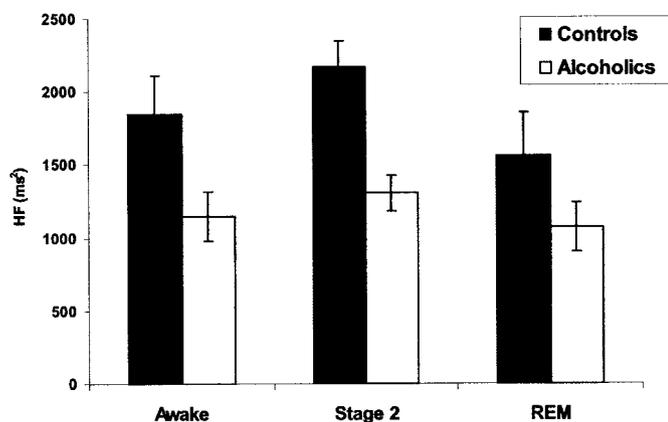


Figure 1. Comparison of the high-frequency (HF; 0.04–0.15 Hz) component of heart rate variability across the night and during awake before sleep, stage 2 sleep, and rapid eye movement (REM) sleep in alcohol-dependent subjects ($n = 14$) and matched comparison control subjects ($n = 14$). Data are mean \pm standard error of mean. Repeated-measures analysis of variance showed a significant group effect with alcoholics having lower levels of the HF power component as compared with control subjects ($F [1, 24] = 5.0, p < .05$), a significant effect for sleep stage ($F [2, 52] = 7.8, p < .001$) but no group-by-sleep-stage interaction.

change in HF power across successive periods of NREM sleep (38), exploratory pairwise comparisons were conducted. As compared with control subjects, alcoholics showed lower levels of HF power during the first period of NREM sleep ($t = 2.5, p < .05$) but not during the second or third NREM periods. For LF power and the ratio of LF/HF, repeated-measures ANOVA showed no significant group effects or interactions across the three sleep stages or across the successive periods of NREM/REM sleep (all p 's $> .05$).

Because alcohol consumption histories and smoking status differed between groups, secondary analyses were conducted to evaluate the relationship of these factors to measures of heart rate variability. Recent alcohol consumption (i.e., time since last drink) was not found to correlate with heart rate or with HF during the awake period before sleep, stage 2, or REM sleep or across the entire night (all p 's $> .1$). Similarly, within the alcohol-dependent group, neither alcohol consumption indices nor severity of alcohol dependence (e.g., number of withdrawal symptoms, duration of dependence as measured by years of alcohol dependence) correlated with heart rate or HF power (all p 's $> .1$).

Smoking status as well as smoking withdrawal are reported to increase sympathetic activity (39). Hence, we evaluated the confounding effects of smoking and/or the possible influence of acute tobacco withdrawal during the experimental protocol on heart rate and HF power. No significant correlations between number of cigarettes used per day and heart rate or HF power at any of the sleep-stage assessments were found (all p 's $> .1$). In addition, when the total sample was stratified by two groups (smokers, $n = 10$; nonsmokers, $n = 18$), neither differences for heart rate nor HF power were found (all p 's $> .1$). Similarly, heart rate and HF power were not different within the alcoholics stratified by smoking status; for example, during waking before sleep, similar levels of HF power were found in the smoker ($n = 8$) and nonsmoker alcohol-

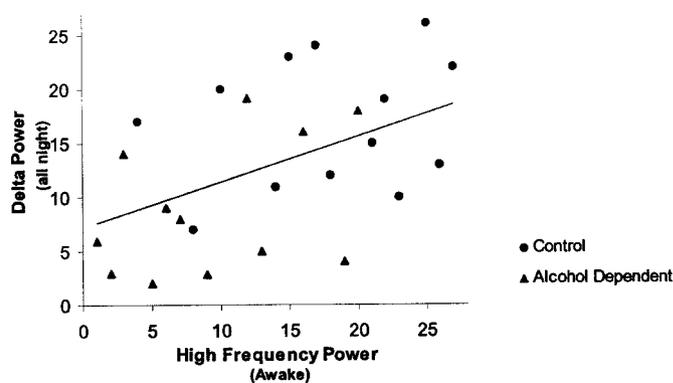


Figure 2. High-frequency (HF; 0.04–0.15 Hz) component of heart rate variability during awake before sleep correlated with delta power across the total night (Spearman's rho = 0.47, $p < .05$).

dependent men ($n = 6$) (1255 ms^2 versus 1123 ms^2 ; $t = 0.52, p = .61$).

Association Between Vagal Tone and Sleep Depth

The relationship between HF power and delta sleep was tested following evidence of group differences in delta sleep and in HF power. HF power during awake before sleep correlated with amounts and percentage of delta sleep (Spearman's rho = 0.43, $p < .05$; Spearman's rho = 0.37, $p = .06$) and delta power (Fig. 2; Spearman's rho = 0.47, $p < .05$). In contrast, neither HF power across the entire night nor during stage 2 or REM sleep correlated with delta sleep amounts, delta percentage, or delta power. Number of awakenings was not correlated with any of the heart rate variability assessments.

Association Between Vagal Tone and Reports of Sleep Impairment

Further analyses examined the relationship between HF power and reports of sleep quality and measures of daytime functioning. HF power during awake before sleep negatively correlated with PSQI measures of sleep quality (Spearman's rho = $-0.48, p < .02$) (Fig. 3) and with 8:00 AM measures of Stanford sleepiness (Spearman's rho = $-0.47, p < .02$) and

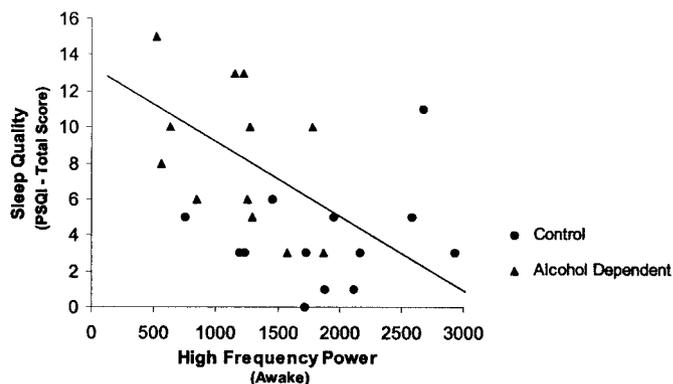


Figure 3. High-frequency (HF; 0.04–0.15 Hz) component of heart rate variability during awake before sleep correlated with sleep quality as measured by total scores on the Pittsburgh Sleep Quality Index (Spearman's rho = $-0.48, p < .05$).

POMS fatigue (Spearman's $\rho = -0.56, p < .001$). HF power during REM sleep also negatively correlated with POMS fatigue (Spearman's $\rho = -0.42, p < .05$) but not with measures of sleep quality, sleepiness, or vigor. HF power during stage 2 sleep was not correlated with measures of sleep quality, sleepiness, fatigue, or vigor; none of the HF assessments correlated with any of the behavioral measures of sleepiness, vigor, or fatigue obtained at 8:00 PM; and none of behavioral measures at either 8:00 PM or 8:00 AM correlated with assessment of delta sleep or delta power.

DISCUSSION

In this study of alcohol-dependent men, a decrease in the vagal tone as indexed by the HF power component was found during the waking period before sleep onset and during nocturnal sleep. Moreover, reduced power in the HF component observed during awake before sleep correlated with subsequent amounts of delta sleep and delta power recorded during sleep, as well as with morning measures of perceived sleep quality and reports of sleepiness and fatigue. These findings provide insight into the effects of alcohol dependence on sympathovagal balance and implicate decreases of vagal tone before sleep as one mechanism that is associated with abnormalities in sleep depth and impairments in morning perceptions of sleep quality and restfulness.

The pathways explaining the association between the HF component and delta power remain unknown. However, the link between delta sleep and levels of vagal tone during the waking period before sleep, but not during sleep, are consistent with the hypothesis that autonomic activation mechanisms interfere with sleep. Bonnet and Arand have found that patients with primary insomnia show increases of the LF component of heart rate variability across the night (25). Furthermore, acute stress blunts nocturnal parasympathetic modulation and interferes with depth of sleep (38). Finally, these findings are also informative about the potential mechanisms that are hypothesized to contribute to insomnia in persons who are withdrawing from other substances. For example, in smokers who are undergoing tobacco cessation, insomnia is a prominent complaint (40), which is coupled with evidence of autonomic dysfunction (41). Yun and colleagues have hypothesized that this shift toward sympathetic bias is a compensatory response that is present in current smokers as well as in those undergoing smoking cessation despite the provagal nature of the nicotinic pathway (41).

The present findings are novel in showing that the level of vagal tone before sleep, but not during or as a consequence of disrupted sleep, is associated with sleep depth. In addition, these findings are the first to our knowledge to show that a low level of vagal activity before sleep correlates with decrements in perceived sleep quality and increases of morning sleepiness and fatigue. However, inference about causality cannot be made given the between-subjects design of this study and these correlational results. Hence, interventions, including behavioral and/or pharmacologic approaches, that target either the parasympathetic or the sympathetic branch of the auto-

nomous nervous system are needed to evaluate whether changes in vagal tone might have salutary effects on sleep depth, sleep quality, and daytime functioning. Indeed, there is evidence that relaxation and biofeedback, which decrease sympathetic dominance and/or increase parasympathetic activity (42,43), are efficacious in the management of insomnia, although the effect sizes are somewhat less robust than cognitive behavioral treatment approaches (44,45). In contrast, pharmacologic treatment of primary insomnia with the hypnotic medication, Zopiclone, has been reported to have no effects on heart rate or EKG activity during sleep (46). Interestingly, acute administration of another class of hypnotic medications, benzodiazepines, leads to acute increases of heart rate and decreases of central vagal tone (47).

Increases of sympathetic tone and/or decreased parasympathetic tone predispose to the occurrence of ventricular arrhythmias such as ventricular fibrillation (48,49), and this mechanism is invoked as one pathway explaining the link between reduced heart rate variability and mortality in patients with heart disease (50). Alcohol dependence is a major risk factor for cardiovascular diseases with alcohol-dependent men showing an increased prevalence of cardiac arrhythmias (51,52), which may be triggered in part by decreased parasympathetic activity. In this study, we have found a withdrawal of parasympathetic activity during awake before sleep and during stage 2/NREM sleep in the alcoholics and an increase in heart rate across the night. We have additionally demonstrated that alcoholics show an exaggerated activation of cardiovascular (i.e., heart rate) and sympathetic nervous system activity in response to sleep loss, which persists even after a full night of recovery sleep (53). Alcohol dependence as well as sleep deprivation are both thought to increase catecholamine release through activation of central nervous system centers and alterations of sympathovagal balance (54–56). Taken together, these studies suggest that alcoholics who experience a night of insufficient sleep may be particularly vulnerable to cardiovascular arrhythmias, which are known to occur more frequently from early morning to noon (57).

Decreases in parasympathetic activity during awake before sleep and nocturnal sleep in alcoholics were found after over 4 weeks of abstinence, suggesting that neither alcohol itself nor acute withdrawal is the cause of the differential loss of vagal tone. Likewise, the severity of alcohol dependence, duration of alcohol dependence, time since last drink, and smoking status were not associated with the HF component in the alcoholics. However, in regard to smoking severity, withdrawal symptoms were not evaluated and the small number of smokers limits conclusions. Differences in the HF component of heart rate variability cannot be attributed to factors such as age, black ethnicity, BMI, or physical activity, because these variables were controlled by generating groups similar on these confounders. Other factors such as physical activity, which can alter sympathovagal balance, were experimentally controlled by restricting all subjects' physical activity during the day and limiting the amount of movement during the nocturnal period to sleeping with the bed flat. This study was

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limited to males, and it is not known whether declines of parasympathetic activity with alcohol dependence are more likely to occur in men as compared with women. Nevertheless, we have reported that men show lower levels of HF power during sleep as compared with women (58), and another study suggests that men show greater declines of parasympathetic activity in response to a visceral stressor as compared with women (59). Finally, the study sample is relatively small, although evaluation of prior effect sizes in planning of this study (15) indicated that a sample of 24 participants is adequate to detect effects of alcohol dependence on EEG sleep. Indeed, the present EEG sleep findings are consistent with our prior results (9,10), although increases rather than decreases in beta activity during NREM sleep were previously reported (10).

In alcoholics, as compared with control subjects, nocturnal increases of heart rate and decreases of parasympathetic activity occur along with a loss of delta sleep and delta power. Decreases of vagal output measured while awake just before sleep may play a role in promoting loss of sleep depth as well as in the onset of cardiac arrhythmias in abstinent alcoholics. Studies are needed to track whether recovery of parasympathetic activity occurs over longer periods of time after periods of abstinence. Moreover, it is not known whether these abnormalities of sleep and sympathovagal balance regulation are a preexisting condition, or trait factor, in alcohol dependence. In fact, insomnia has been suggested to be a risk factor for the development of alcohol dependence (60). Studies of insomniacs who are not currently alcohol-dependent have shown that insomniacs find alcohol more reinforcing than control subjects, in which alcohol also reduces feelings of "tension" during the time before sleep onset (61). Therefore, targeting interventions that can reduce "tension," autonomic activation, or central arousal states during the time before sleep onset may be found to be efficacious in the prevention of alcohol dependence in vulnerable individuals. Future studies should also explore the potential reversibility of these abnormalities of sleep and sympathovagal functioning in alcohol dependence, and whether treatments that increase vagal tone might ameliorate sleep disturbance and risk for relapse in alcohol-dependent individuals.

The authors thank Ivonne Chand O'Neal and Julie Kim for assistance in participant recruitment and study coordination, and Jessica Lee for data management and statistical analyses.

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