

Sleep Deprivation Potentiates Activation of Cardiovascular and Catecholamine Responses in Abstinent Alcoholics

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Abstract—Alcohol dependence is associated with an increased incidence of hypertension and cardiac arrhythmias, but the triggering mechanisms are not known. Sleep loss, common in alcohol-dependent patients, causes an activation of the sympathetic nervous system. To determine whether sleep deprivation induces differential cardiovascular and sympathetic responses in alcohol dependence, we measured heart rate, blood pressure, and circulating sympathetic catecholamines in 36 abstinent alcohol-dependent men and 36 age-, gender-, and ethnicity-matched controls after a baseline night of sleep, in the morning after early night partial sleep deprivation, and again after a full night of recovery sleep. Subjects were on average normotensive and none was being treated for hypertension. Baseline heart rate, blood pressure, and sympathetic catecholamines were similar in the 2 groups. Administration of partial night sleep deprivation induced greater increases of heart rate ($P<0.01$) and circulating levels of norepinephrine ($P<0.05$) and epinephrine ($P<0.05$) in the alcohol-dependent men as compared with responses in controls. Even after a full night of recovery sleep, elevations in heart rate ($P<0.05$) and circulating catecholamines ($P<0.05$) persisted in the alcoholic subjects. Partial night sleep deprivation induces elevated heart rate and sympathetic catecholamine responses in alcoholic subjects as compared with controls, and this sympathetic activation is sustained after nights of partial and recovery sleep. It is possible that modest habitual sleep loss could contribute to triggering cardiac arrhythmias or other cardiovascular events in alcohol dependence. (*Hypertension*. 2005;45:252-257.)

Key Words: alcohol ■ cardiovascular disorders ■ sleep ■ catecholamine

Alcohol dependence, which exceeds a lifetime incidence of 10%,¹ is a major risk factor for cardiovascular diseases, with alcohol-dependent men showing an increased prevalence of hypertension and cardiac arrhythmias.^{2,3} An increase of sympathetic nervous system activity is implicated as being one underlying mechanism of the deleterious cardiovascular effects of chronic alcohol consumption.⁴ Human studies have found that acute alcohol intake induces elevations of heart rate and blood pressure via centrally mediated increases of sympathetic discharge.⁵ There is also evidence that abnormalities of cardiovascular regulation persist into recovery. Abstinent alcohol-dependent male patients show exaggerated heart rate and blood pressure reactivity in response to behavioral stress, although measures of sympathetic activation have not been determined.⁶⁻⁸ In this study, we examined cardiovascular responses and circulating levels of norepinephrine and epinephrine at rest and in response to a behavioral challenge, sleep deprivation, in abstinent male alcohol-dependent patients.

Experimental sleep deprivation can serve as a naturalistic probe of the homeostatic regulation of sympathetic activity. Loss of sleep induces elevations in circulating levels of epinephrine and norepinephrine,^{9,10} with attendant increases of blood pressure and heart rate the next day.^{11,12} In addition,

habitual sleep loss and insomnia are markers of subclinical heart disease and are independent predictors of cardiovascular disease risk, particularly in males.¹³ Fluctuations in sympathetic activity across the sleep-wake cycle are thought to contribute to the low rates of sudden cardiac death, myocardial infarction, and ischemic stroke during sleep, as well as to their peak incidence at the end of sleep or in the morning after awakening.¹⁴

In alcohol-dependent persons who show abnormalities of sleep continuity and sleep depth at rest,¹⁵⁻¹⁷ administration of sleep deprivation reveals a defect in these patients' ability to recover from even a modest loss of sleep.¹⁶ For example, in contrast to the robust recovery of delta sleep found in controls, abstinent alcohol-dependent patients do not generate increases of deep delta sleep after early night partial sleep deprivation (PSD-E).¹⁶ In this study, we tested the hypothesis that early night sleep deprivation will induce sympathetic activation in abstinent alcohol-dependent men, and that increases of heart rate, blood pressure, and circulating levels of sympathetic catecholamines will be sustained after recovery sleep in alcoholic subjects as compared with responses in age-, gender-, and ethnicity-matched controls. Subjects were on average normotensive and none was receiving hypertensive medications.

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Materials and Methods

Human Subjects

Alcoholic patients were hospitalized for 2 weeks in the Alcohol and Drug Treatment Program at the Veterans Affairs San Diego Health-care System (VASDHS) before screening evaluation. Nonpatient controls were recruited by advertisements and direct mailing to the San Diego County veteran population. Alcoholic patients fulfilled Diagnostic and Statistical Manual IV (*DSM-IV*) criteria for alcohol dependence that had occurred in the absence of major pre-existing or concomitant psychiatric disorders,¹⁸ including secondary depression.¹⁹ Control subjects fulfilled *DSM-IV* criteria for "never mentally ill."¹⁸

A total of 99 men fulfilled screening eligibility criteria, gave informed consent, and entered the research protocol. Of this total, 6 participants were excluded because of medical history and/or medication use, 2 controls and 4 alcoholic subjects were released from the study because of positive toxin screens during the sleep protocol or within the 2-week period before assessment, 7 subjects were excluded because of nocturnal myoclonus, 2 alcoholic subjects were excluded because of decreased oxygen saturation during sleep, and 3 controls and 3 alcoholic subjects did not complete blood sampling. The remaining sample comprised 72 men (36 control subjects, 36 alcoholic patients). All participants were in good health as determined by medical history and laboratory screening blood tests. None fulfilled criteria for primary substance dependence or had used substances in the past 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 using medications known to alter sleep wake activity (eg, β -blockers, psychotropic medications) within 2 weeks of the sleep protocol. Alcoholic subjects were studied after acute and subacute withdrawal symptoms had resolved; 2 alcoholic patients had been treated with diazepam 30 days before study. Nursing observations and random urine substance screens were used to confirm abstinence during the sleep protocol. Further details about recruitment, diagnostic evaluation procedures, and subjects' health have been reported previously.^{16,17}

Procedures

Details about the sleep screening, sleep protocol, and EEG sleep methods have been previously described^{16,17} and are also found in the online supplement (<http://www.hypertensionaha.org>).

For assessment of heart rate and blood pressures, supine resting measures were limited to the morning immediately after awakening; all-night blood pressure monitoring has been found to induce declines of sleep amounts and depth. While subjects remained in the supine position, heart rate was monitored with an ECG and blood pressure was assessed using a blood pressure monitor (Dinamap 1846 SX-P; Critikon, Tampa Bay, Fla) that had been validated within 5 mm Hg of a standard mercury sphygmomanometer. Data on heart rate and blood pressure were obtained from the mean of 3 separate measures taken 5 minutes apart in the first 15 minutes after waking.

For assay of plasma catecholamines, blood sampling was performed twice at 23:00 hours before "lights out" and at 06:30 hours before awakening via an intravenous catheter that has not been found to alter sleep amounts or depth.^{15,20} Catecholamines were assayed as previously described.²¹

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 >95% of their data. Group differences in age, education, body mass index, alcohol consumption histories, and liver function tests were tested using 1-way ANOVAs. To evaluate group and night differences in EEG sleep measures, heart rate, and blood pressure, repeated measures ANOVAs were performed using a 2 (group: alcoholic subjects, controls) \times 3 (night: baseline, PSD-E, recovery) design. Circulating levels of epinephrine and norepinephrine were log-

transformed to achieve a normal distribution. To evaluate group, night, and time differences in circulating levels of plasma catecholamines, repeated measures ANOVAs were performed using a 2 (group) \times 2 (time: 23:00 hours, 06:30 hours) \times 3 (night) design. Two covariates, age and ethnicity (white; black), were added a priori to the ANOVA models given evidence that age and black ethnicity are associated with greater catecholamines levels and/or responsiveness to behavioral challenge.^{22,23} It was not appropriate to include body mass index as a covariate, given the causal effects of chronic alcohol use to reduce body fat mass,²⁴ as well as the high correlations between alcohol consumption and body mass index. The possible confounding influence of body mass index on cardiovascular responses and circulating catecholamines was tested by zero order correlations.

Based on a priori hypotheses, planned comparisons were performed to determine whether administration of sleep deprivation led to increases of cardiovascular responses and norepinephrine and epinephrine in alcoholic subjects as compared with controls. It should be noted that these planned comparisons do not require a significant omnibus F finding to be evaluated appropriately. According to Keppel,²⁵ an unprotected analytic comparison of group differences only occurs when no a priori hypotheses exist or a nonsignificant omnibus F finding is obtained.

Results

The 2 groups were similar in age, ethnicity, and depressive symptom severity, yet differed on education, body mass index, and alcohol and tobacco consumption histories (Table). EEG sleep results are described in the supplement.

Measures of heart rate and blood measures were obtained the morning after each of the 3 nights: baseline, PSD-E, and recovery. For heart rate, there was a significant night effect [$F(2, 130)=21.4, P<0.001$] and a significant group \times time interaction [$F(2, 126)=6.1, P<0.01$; Figure 1A]. There was no group effect. Planned group comparisons tested whether sleep deprivation would lead to increases of heart rate at the 6:30-hour time point in alcoholic subjects as compared with controls. Alcoholic subjects and controls had similar heart rate after baseline night [$F(1, 64)=1.9, P=0.17$], whereas morning heart rate was higher in alcoholic subjects than controls after PSD-E [$F(1, 64)=5.9, P<0.01$] and recovery nights [$F(1, 64)=3.3, P<0.07$]. There was a significant night effect for systolic blood pressure [Figure 1B; $F(2, 130)=27.2, P<0.001$] and for diastolic blood pressure [$F(2, 130)=19.5, P<0.001$], in which sleep deprivation induced similar increases of blood pressure in both groups, which were maintained after recovery sleep. There was neither group effect nor group \times night interaction for either measure of blood pressure.

Across the 3 nights, circulating levels of norepinephrine were higher in alcoholic subjects as compared with controls with an overall group effect [$F(1, 68)=4.0, P<0.05$; Figure 2A]. In addition, norepinephrine showed a night effect [$F(2, 136)=6.0, P<0.01$] with significant increases after sleep deprivation. There was no time effect or interactions for norepinephrine. Alcoholic subjects and controls had similar levels of norepinephrine at 6:30 hours after the baseline night [$F(1, 68)=0.5, P=0.47$]. In contrast, after the PSD-E and recovery nights, morning levels of norepinephrine were higher in alcoholic subjects than controls [$F(1, 68)=3.5, P=0.05$; $F(1, 68)=5.8, P<0.05$].

Similar to the findings for norepinephrine, circulating levels of epinephrine were also higher in the alcoholic subject as compared with the controls across the 3 nights [group effect: $F(1, 67)=4.6, P<0.05$; Figure 2B]. Epinephrine significantly

Age, Ethnicity, Education, Body Mass Index, Severity of Depressive Symptoms, and Alcohol and Tobacco Consumption Histories in Control and Alcohol-Dependent Groups

Variables	Control (n=36)		Alcohol-Dependent (n=36)		Alcoholism Effect	
	Mean	SD	Mean	SD	F	P
Age, y	43.6	9.9	43.5	9.2	0.0	0.96
Education, y	15.0	1.5	13.2	1.5	26.1	<0.001
Body mass index*	23.9	3.4	22.0	2.4	8.0	<0.01
Depressive symptoms, HDRS scores	1.3	1.7	1.7	2.1	0.9	0.36
Alcohol consumption, past 3 months						
Drinking						
Drinks per month	6.1	8.5	26.9	5.0	160.6	<0.001
Drinks per day	2.0	3.9	13.2	10.1	38.5	<0.001
Days since last drink	74.3	135.5	21.0	9.9	5.6	<0.02
	N	%	N	%	χ^2	P
Black	14	39	14	39	0.0	0.98
Tobacco smokers	3	8	20	56	22.3	<0.001

HDRS indicates Hamilton Depression Rating Scale. **Boldface** refers to significant results.

*Body mass index=weight in kilograms/height in square meters.

changed across the individual nocturnal periods with a time effect [$F(1, 67)=7.1, P<0.05$]. There was no main effect for night, and no significant interactions for epinephrine. During the baseline night, alcoholic subjects and controls had similar nocturnal levels of epinephrine [$F(1, 67)=1.9, P=0.18$]. In

contrast, morning levels of epinephrine were significantly higher in alcoholic subjects than controls after PSD-E [$F(1, 67)=4.4, P<0.05$] and recovery [$F(1, 67)=4.6, P<0.05$].

The significant differential increases of heart rate and catecholamine responses to PSD-E in abstinent alcoholic subjects

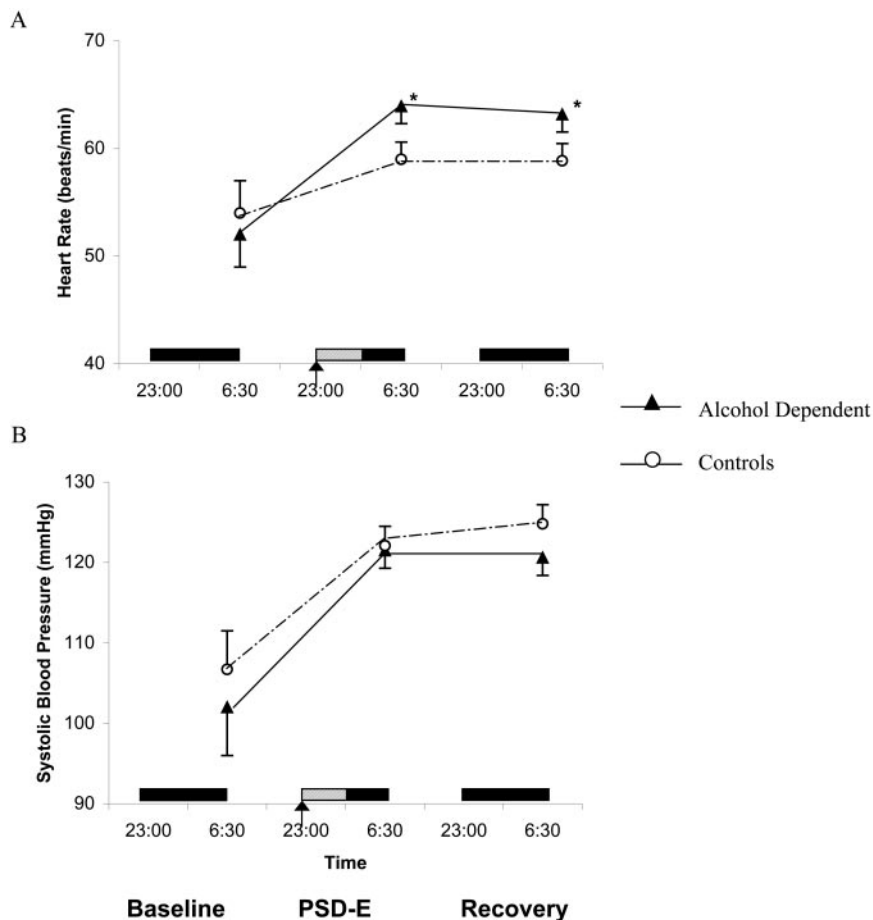


Figure 1. Comparison of heart rate measurements in beats per minutes (A) and systolic blood pressure in mm Hg (B) the morning after baseline sleep, early night partial sleep deprivation (PSD-E), and recovery sleep in alcohol-dependent subjects (n=36) and matched comparison controls (n=36). The solid shaded area indicates nocturnal sleep, and the vertical arrow followed by the hatched shaded area indicates the nocturnal period of sleep deprivation. Time is expressed using a 24-hour clock. Data are mean±SEM. *Significant differences between the alcohol-dependent and control groups at $P<0.05$.

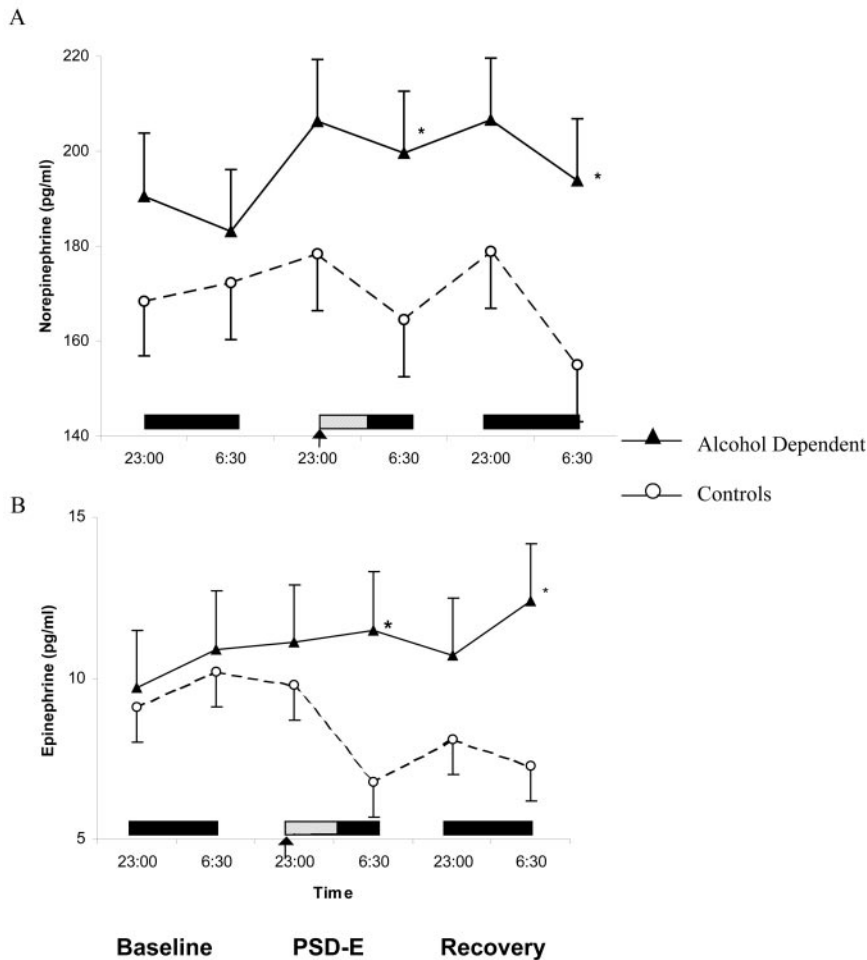


Figure 2. Comparison of circulating levels of norepinephrine (A) and epinephrine (B) (in pg/mL) immediately before and after baseline sleep, early night partial sleep deprivation (PSD-E), and recovery sleep in alcohol-dependent subjects (n=36) and matched comparison controls (n=36). The solid shaded area indicates nocturnal sleep, and the vertical arrow followed by the hatched shaded area indicates the nocturnal period of sleep deprivation. Time is expressed using a 24-hour clock. Data are mean \pm SEM. *Significant differences between the alcohol-dependent and control groups at $P < 0.05$.

were present when age and black ethnicity were covaried. Neither education nor age correlated with measures of cardiovascular or sympathetic function at any of the time points. The influence of smoking status on cardiovascular and catecholamine responses was tested by additional analyses that stratified the alcoholic subjects into groups of smokers (n=19) and nonsmokers (n=17). There were no main effects of smoking status or interactions for measures of heart rate, systolic blood pressure, diastolic blood pressure, or plasma levels of norepinephrine or epinephrine within the alcoholic subjects (all $P > 0.1$). Furthermore, within the smokers, correlations were nonsignificant between number of cigarettes used per day and cardiovascular measures or plasma catecholamines at any of the time points (all $P > 0.1$). Finally, previous evidence has shown that alcoholic subjects with elevated blood pressure show greater reactivity to behavioral challenge;⁶ thus, we explored whether alcoholic subjects who differed in blood pressure before the sleep protocol showed differential cardiovascular and sympathetic responses after sleep deprivation. Three subgroups of alcoholic subjects were identified: normotensive (n=21; systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg); prehypertensive (n=10; systolic blood pressure 120 to 139 mm Hg or diastolic blood pressure 80 to 89 mm Hg); and stage 1 hypertensive (n=5; systolic blood pressure 140 to 159 mm Hg or diastolic blood pressure 90 to 99 mm Hg). Although the normotensive and hypertensive groups showed

similar blood responses after sleep loss, epinephrine levels after the recovery night, but not baseline or PSD, were significantly elevated in alcoholic subjects with stage 1 hypertension [$F(1, 25) = 5.2, P < 0.05$] or with stage 1 hypertension or prehypertension [$F(1, 35) = 5.8, P < 0.05$] as compared with normotensive alcoholic subjects. Levels of norepinephrine were similar for the groups across each of the nights.

Discussion

Early night sleep loss resulted in elevated heart rate and levels of norepinephrine and epinephrine in male alcohol-dependent patients as compared with controls. Even after a full night of recovery sleep, alcoholic subjects continued to show an elevated heart rate and morning catecholamine levels. Thus, alcoholic subjects do not recover from the effects of even a modest loss of sleep, which influences heart rate and might alter tremor²⁶ and cardiac arrhythmias.³ Increases in sympathetic tone have been implicated in triggering cardiovascular events in the morning.^{11,27}

These data extend previous studies of blood pressure reactivity in alcohol-dependent patients,⁶⁻⁸ and this is the first study to our knowledge that has examined alterations of circulating catecholamines at rest and in response to a behavioral challenge in alcoholic subjects. In male alcoholic subjects who have transient hypertension during alcohol withdrawal,⁶⁻⁸ administration of a behavioral stressor-induced greater blood pressure

increases as compared with controls. Likewise, in women who have had transitory withdrawal hypertension, there is evidence of persistent cardiovascular dysregulation in which diastolic blood pressure is elevated during 2 aversive stressors, hand grip and public speaking, despite normal resting levels.²⁸ In contrast, one other study found that alcohol-dependent patients show a blunted blood pressure response to public speaking stress, although this alteration was thought to be caused by a blunted perception of the social threat at the level of the central nervous system.²⁹ In the present study, no differential change in blood pressure was found in the 2 groups, with alcoholic subjects and controls showing similar increases of blood pressure in response to sleep loss. However, to allow for comparison of the effects of alcohol dependence on cardiovascular responses without the confounding effects of hypertensive medications, this study excluded alcoholic subjects who were currently being treated for hypertension. Thus, it is possible that these criteria identified alcoholic subjects who are resistant to exaggerated blood pressure reactivity. Alternatively, hospitalization is known to promote decreases of resting blood pressure, and we speculate that alcoholic subjects dwelling in the community might show differential increases of blood pressure after sleep loss. Nevertheless, in exploratory analyses, we report that alcoholic subjects with prehypertension and/or stage 1 hypertension showed exaggerated increases of epinephrine during recovery from sleep loss as compared with normotensive alcoholic subjects.

Sleep deprivation and disordered sleep lead to daytime overproduction of proinflammatory cytokines,^{15,20} which are also implicated in the risk for cardiovascular disease.³⁰ We have previously reported that alcoholic subjects show nocturnal elevations of IL-6 and tumor necrosis factor (TNF), which are further exacerbated by sleep deprivation.³¹ However, the mechanisms that underlie changes in inflammatory cytokines in alcoholism are not known; for example, we found no correlation between measures of circulating catecholamines and plasma concentration of IL-6 or TNF in a subsample of alcoholic subjects and controls ($n=27$) reported here. Alternatively, increases of vagal tone are associated with declines in the production and circulating levels of TNF.³² Van Cauter et al have suggested that "sleep debt" induces alterations of sympathovagal balance with metabolic and immunologic effects, including increases in expression of proinflammatory cytokines.³³ Further study of autonomic regulation is needed to determine whether changes in sympathovagal balance lead to the overexpression of proinflammatory cytokines in alcoholic subjects.

Alcohol intake is one of the factors known to increase blood pressure levels,³⁴ and the increased morning surge in blood pressure is associated with cardiovascular events in hypertensive patients.³⁵⁻³⁷ However, findings from the present sample of alcohol-dependent men do not necessarily generalize to mild to moderate chronic alcohol intake, which has been associated with slight favorable effects on cardiovascular events in healthy adults.³⁸

Elevated sympathetic responses in alcoholic subjects were found after >3 weeks of abstinence, suggesting that pharmacological action of alcohol is not the cause of these differential responses. In addition, differences in heart rate and catecholamine responsiveness to sleep loss cannot be attributed to factors

such as age or black ethnicity, because both of these variables were controlled by matching the 2 groups and by statistical covariance. Whereas it is possible that differences in cigarette smoking histories between the alcoholic subjects and controls could be related to these findings, resting baseline levels of catecholamines before sleep deprivation did not differ between the groups, and smoking status within the alcoholic subjects had no impact on cardiovascular or catecholamine responses. Moreover, the pharmacological effect of nicotine on sympathetic activity was minimized by the assessment of morning levels of epinephrine and norepinephrine after >8 hours since last use of nicotine. Other factors such as physical activity that can alter sympathetic measures were experimentally controlled by restricting all subjects to the supine position across the nocturnal periods. Potential confounders such as education and body mass index were not correlated with measures of epinephrine or norepinephrine at any time point. Finally, in contrast to the differential effects of sleep loss, there was no relationship between sleep architecture measures (eg, delta sleep, rapid eye movement sleep) and measures of cardiovascular and catecholamines on any of the nights.

Given evidence that acute sleep loss and chronic sleep debt alter autonomic, metabolic, and immune functioning,^{10,20,33,39} the present data indicate that chronic habitual sleep disturbance may have pathophysiological consequences in alcohol dependence. Difficulties with sleep onset and maintenance show a protracted course and persist for months to years after abstinence in recovering alcoholic subjects.⁴⁰ Second, the physiological effects of sleep loss in alcoholic subjects might be further perpetuated by a failure of sleep recovery.¹⁶ Third, sleep loss induces exaggerated increases of IL-6 and TNF, which persist after recovery sleep in alcoholic subjects.³¹ Increases in the expression of inflammatory markers are implicated in the risk of cardiovascular disease and inflammatory and infectious disorders.³⁰ Fourth, alcohol dependence, as well as sleep deprivation, are thought to increase catecholamine release through activation of central nervous system centers and alterations of sympathovagal balance.^{11,27,41,42} Alcoholic subjects who have a night of insufficient sleep may be particularly vulnerable to increases of blood pressure and heart rate in the morning.^{11,12} Cardiovascular events are known to occur more frequently from early morning to noon,¹⁴ and longitudinal studies have found that autonomic dysregulation is related to greater risk of cardiovascular disease.⁴³

Perspectives

Sleep deprivation induces elevated heart rate and catecholamine responses in alcoholic subjects as compared with controls, which are sustained after nights of partial and recovery sleep. Increased sympathetic nervous activity that occurs along with habitual sleep loss may play a role in tremor, anxiety, hypertension, and cardiac arrhythmias of abstinent alcoholic subjects.

Studies need to be performed to track recovery of sympathetic activity or lack of recovery over longer periods of time in alcohol dependence. Moreover, it is not known whether these abnormalities of sleep and sympathetic regulation are pre-existing, as might be found in the offspring of alcoholic subjects. Future studies should also explore the potential

reversibility of these abnormalities of sleep and physiological functioning in alcohol dependence. Behavioral treatments, which are highly efficacious for the treatment of chronic insomnia,⁴⁴ may ameliorate abnormalities in sleep and sympathetic reactivity in alcohol dependence.

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