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Poor autonomic nervous system functioning during sleep in recently detoxified alcohol-dependent men and women

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Abstract

Background—Alcoholism is considered an important risk factor for cardiovascular disease. Autonomic nervous system (ANS) function is a major indicator of cardiovascular health. Sleep is a suitable model to investigate ANS activity free from wake-related confounders. We investigated night-time ANS functioning, and the relationship between ANS activity and severity of alcohol dependence in chronic alcoholism.

Methods—Fourteen recently abstaining alcoholics (Age: 42.0±9.0y, 7 women) and sixteen age- and sex-matched controls (Age: 45.2±9.1y, 8 women) underwent a night of standard clinical polysomnography, including electrocardiographic recording. Time- and frequency-domain spectral analysis of heart rate variability (HRV) was performed across hours of the night and during artifact-free epochs of stable sleep and wakefulness (pre-sleep wakefulness, rapid-eye-movement (REM) and non-REM sleep).

Results—Alcoholics had a poorer subjective and objective sleep quality compared to controls. Across the night, alcoholic men and women had elevated heart rate, reduced total HRV, i.e. lower standard deviation of normal-to-normal inter-beat-intervals, and reduced high frequency activity (assessed by the high frequency power and by the square root of the mean squared of successive heart period differences). This ANS pattern was most apparent at the beginning of the night. None of the ANS measures was associated with lifetime alcohol consumption or duration of alcohol dependence.

Conclusions—Our results show that ANS functioning is disrupted during the night, even in undisturbed sleep periods, indicating poor cardiovascular functioning in recently detoxified alcohol-dependent men and women.

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Keywords

Alcoholism; autonomic nervous system; heart rate variability; sleep

1. Introduction

Alcoholism is a dramatic polypathology affecting millions of people, with more than 10% of US citizens meeting the DSM-IV lifetime alcohol dependence criteria (Hasin and Grant, 2004). Alcoholism is considered an important risk factor for many health problems, of which cardiovascular (CV) disease is one of the most common (Rehm, 2011).

The CV system is under control of both the sympathetic and parasympathetic branches of the autonomic nervous system (ANS). A number of autonomic function tests (e.g., pupil cycle time, blood pressure and heart rate responses to Valsalva maneuver, to deep breathing or to standing) indicate disturbance to the ANS, particularly the vagal division, in chronic alcoholism (Barter and Tanner, 1987; Duncan et al., 1980; Johnson and Robinson, 1988; Matikainen et al., 1986; Miralles et al., 1995; Monforte et al., 1995; Villalta et al., 1989). These effects may mediate the association between alcoholism and increased risk for CV morbidity and mortality.

ANS modulation can be assessed by using heart rate variability (HRV) analysis, a validated method largely used in CV psychophysiology as a tool to investigate the relation between elevated sympathetic or reduced vagal ANS activity and CV adverse events (Barron and Lesh, 1996; Curtis and O'Keefe Jr, 2002). A major advantage of this technique is that it is minimally intrusive and thus particularly well-suited for application during sleep. Two main approaches are used to analyze heart rate derived from an EKG signal based on time and frequency domain metrics (Camm et al., 1996). The time domain method derives measures reflecting the variance in heart rate, such as the standard deviation of the normal beat-to-beat intervals (SDNN), or, the square root of the mean squared of successive heart period differences (RMSSD) (thought to index the influence of the vagus nerve on HRV). In contrast, the frequency domain method decomposes the variance of the total heart period in specific frequency bands. The most common approach applies a Fast Fourier Transformation (FFT) on the time series of beat-to-beat intervals (IBIs) and calculates the power spectrum of low (LF, 0.04-0.15 Hz) and high (HF, 0.15-0.4 Hz) frequencies. The variability in the HF component is an accepted measure of vagal sinoatrial control when breathing is controlled whereas the LF component is considered a mixture of both sympathetic and parasympathetic influences. Another frequency domain measure used is the low-to-high frequency ratio (LF/HF), which is considered to reflect sympathovagal balance. All these measures have been used to assess cardiac functioning (for a review of their meaning and use, see Camm et al., 1996).

Low total HRV is a feature of chronic alcoholism (Ingjaldsson et al., 2003; Rechlin et al., 1996; Yokoyama et al., 1991) and as suggested by Angelink et al. (1998), total HRV seems to be more sensitive than conventional autonomic tests for detecting evidence of cardiovagal dysfunction in chronic alcoholics. Furthermore, a recent meta-analysis confirmed the impact

of alcohol dependence on resting HRV (Quintana et al., 2013) and underlined the importance in reducing CV risk in alcoholic patients.

The acute intake of ethanol in healthy adults as well as in alcoholics is known to decrease total HRV, reduce HF activity and enhance sympathetic dominance of sympathovagal balance during both daytime wakefulness (Johnson et al., 1986; Koskinen et al., 1994; Murata et al., 1994; Reed et al., 1999; Weise et al., 1986) and night-time sleep (Sagawa et al., 2011). The ANS imbalance in alcoholics is also present during alcohol withdrawal (Bär et al., 2006) and seems to be maintained in recently sober alcoholics (Malpas et al., 1991; Pitala et al., 2000; Yokoyama et al., 1991) although others have reported improvements in ANS measures with prolonged periods of abstinence (Hirsch et al., 1993; Tan et al., 1984; Villalta et al., 1989). In addition, the severity of the ANS dysfunction in alcoholism has been found to be associated with the life time alcohol consumption and the duration of alcohol dependence (Monforte et al., 1995; Rechlin et al., 1996; Villalta et al., 1989).

To our knowledge, only two studies have investigated ANS activity during sleep in abstinent alcoholics (Ganesha et al., 2013; Irwin et al., 2006) and only one of these studies (Irwin et al., 2006) used polysomnography to confirm sleep stages. The advantage in studying the ANS during sleep is that sleep is relatively free of external disruptive events (Brandenberger et al., 2005), and thus provides a more accurate measure of basal autonomic activity (Orr et al., 2000). However, sleep is not a uniform state with regard to CV activity. NREM sleep is characterized by lower heart rate, and a higher HF power component of HRV, compared with wakefulness (Trinder et al., 2001). These changes are reversed during REM sleep in which heart rate is higher, and HF power is lower than in NREM sleep (Trinder et al., 2001).

Irwin and colleagues (2006) found that HR was higher and HF power was lower but the LF/HF ratio was similar during pre-sleep wakefulness, stage 2 and REM sleep in alcohol-dependent male patients, who had been abstinent for at least 2 weeks, compared to healthy male controls. Ganesha and colleagues (2013) reported that alcoholic men studied five days after detoxification showed lower SDNN (reduced total HRV), RMSSD and pNN50 (interpreted as time domain vagal measures) as well as lower LF, HF and total HRV power (frequency domain measures) with no difference in LF/HF ratio during the night compared to healthy controls. Both of these studies interpreted their data as showing a reduction in vagal activity in alcoholics compared with controls.

The purpose of the present study was to investigate ANS activity over the whole night and during polysomnographic (PSG)-defined sleep stages across the night in recently detoxified alcoholics and healthy controls. Time domain analysis was used to investigate overall nocturnal HRV, irrespective of awakenings, arousals, or sleep stage. Frequency-domain HRV analyses of artifact-free sleep stages (NREM, REM) was used to investigate ANS activity in undisturbed sleep. Few previous studies have included female alcoholics, so exploratory analyses were conducted to assess possible sex differences within alcoholics.

2. Materials and Methods

2.1. Participants

Twenty-one patients undergoing treatment for alcohol dependence were recruited from residential treatment centers around the San Francisco Bay Area. Nineteen controls were recruited from the community through flyers and announcements. Inclusion criteria in the alcoholic group were: recently sober (≤1 month) and meeting DSM-IV-TR criteria (American Psychiatric Association, 2000) for alcohol dependence for at least 3 years. Controls were age- and sex matched to the alcoholics and had no current Axis I psychopathology. Exclusion criteria were the self-reported use of cardiac medications, severe medical conditions (e.g. hypertension, liver diseases, atherosclerosis, heart disease, ischemic strokes), withdrawal symptoms (e.g. hallucinations, irritability, fatigue, headache, loss of appetite, tremor, fever, convulsion), use of psychotic medications (e.g. antidepressants, anxiolytics), head injury and associated loss of consciousness >30 minutes, as assessed during the structured clinical interview. From the clinical PSG assessment we excluded participants with obstructive sleep apnea or severe periodic limb movements (PLMS) (apneas-hypopneas index, AHI >5 and PLMS index, PLMSI >10); insufficient sleep to enable analysis of heart rate variability.

From the original sample, eight alcoholics were excluded due to severe PLMS (N=3), sleep apnea (N=2), use of antipsychotic medication at the overnight recording (N=2), extremely poor sleep efficiency (3SD below the average value of the group, N=1). Three controls were excluded due to extremely poor sleep efficiency (3SD below the average value of the group). Fourteen recently detoxified alcohol-dependent men and women (7 male, age range: 28-54 y) and 16 healthy individuals (8 male, age range: 30-62 y) constituted the final sample. Demographic measures and alcohol history are provided in Table 1. None of the participants reported past or current severe medical conditions, or were currently using medications known to affect sleep or CV functioning. Seven alcoholics also met the DSM-IV-TR criteria (American Psychiatric Association, 2000) for nicotine dependence, two for cannabis dependence and one for cocaine dependence. Only one of the controls was a smoker (10 cigarettes/day).

This study was approved by the Institutional Review Board at SRI International. All participants read and signed an informed consent form and were paid for participating in the study.

2.2. Procedures

Potential participants were administered a structured alcohol history (Pfefferbaum et al., 1988) and structured clinical interview for Axis I DSM IV Disorders (SCID) (First et al., 1994). Participants also completed the Pittsburgh sleep quality index (PSQI) (Buysse et al., 1989), a 19 items questionnaire measuring sleep disturbance and usual sleep habits during the prior month. Participants rated each item on a 0-3 Likert scale. Higher global scores reflect more sleep complaints and disturbed sleep.

Following the diagnostic interviews, participants were scheduled for a clinical overnight PSG recording in the SRI International sleep laboratory. All alcoholics were in treatment

centers at the time of study. All participants registered 0.0 on a breathalyzer on the evening of their recording.

2.3. Polysomnography

Clinical PSG recordings comprising electroencephalographic (EEG; 256 Hz sampled, 0.3-35 Hz filtered; 4 leads: C3-M2, C4-M1, O1-M2, O2-M1), submental electromyographic (EMG; 256 Hz sampled, 10-100 Hz filtered), bipolar electrooculographic (EOG; 256 Hz sampled, 0.3-35 Hz filtered; E1-E2) measures were made using E-series system and ProFusion PSG software (Compumedics, Abbotsford, Victoria, Australia). Additional clinical measures included breathing effort (chest and abdominal expansion), air flow and pressure (thermistor and nasal cannula), oxygen saturation (pulse oximetry), and bilateral anterior tibial EMG recordings. Objective measures of sleep quality and quantity were derived from the manual scorings of PSG traces according to the standard rules of the *American Academy of Sleep Medicine* (AASM) (Iber C et al., 2007): Wake, N1, N2, N3 and REM sleep stages were assigned to each of the 30-s epochs across the whole night. In addition, arousals from sleep (≥3 s, <15 s) were scored according to standard criteria (Iber C et al., 2007). The following parameters were obtained: time in bed (TIB; min) coincident with the total recording time (TRT, from “lights out” to “lights on”); total sleep time (TST; min); sleep efficiency (SE; %) calculated as the percentage of TST/TIB; sleep onset latency (SOL; min), i.e. the time from the “lights out” to the first epoch of any sleep stage; REM latency (REML; min), the time from sleep onset to the first epoch of REM; wake after sleep onset (WASO; min), time spent awake during TIB minus SOL; duration of each sleep stage (N1, N2, N3, and REM; %), percentage of the time in each stage (min) divided by TST; total number of arousals; total numbers of awakenings after SOL; and fragmentation index, i.e. the total number of sleep stage transitions divided by TIB.

2.4. Assessment of autonomic activity

Autonomic measures were calculated using both time and frequency domain HRV spectral analysis of electrocardiogram (EKG) signals with dedicated software (Sleep Research System, SRS; Melbourne School of Psychological Sciences, University of Melbourne, Australia) and according to established guidelines (Camm et al., 1996). EKG was recorded through Meditrace Ag/AgCl spot electrodes in lead II Einthoven configuration using E-series amplifiers (Compumedics, Abbotsford, Victoria, Australia). The EKG signal was sampled at 512 Hz and 0.3-70 Hz filtered. The ‘R’ peak of each QRS complex of the EKG were automatically detected (and then visually inspected) by an automated algorithm allowing the software to calculate the inter-beat-intervals (IBIs) in milliseconds (ms). A further visual inspection allowed the identification and interpolation of missed and ectopic beats.

Frequency-domain HRV analysis was performed on artifact-free 2-min epochs selected from a pre-sleep wakefulness period after lights-out and throughout the night according to specific and validated rules previously described by Trinder and colleagues (2001). The following dependent variables were obtained: total power (ms^2), heart rate (HR, bpm) derived from the IBIs, power in HF (HF_a, arbitrary units) reflecting vagal functioning, the frequency of the HF peak (HF_p, Hz) considered a measure of respiratory rate, and the ratio

of low-to-high frequency activity (LF_a/HF_a ratio), a measure of sympathovagal balance. Variables were averaged for the pre-sleep wakefulness period, and separately for NREM (Stage N2 and N3, combined), and REM sleep.

Time-domain HRV analysis was performed on consecutive 5-min epochs. The epochs were then averaged over 60 minute periods across the first 6 hours of the night from lights-out since all participants had at least 6 hours in bed. Time domain analysis was performed on epochs irrespective of sleep stage, arousals, or periods of wakefulness.

Heart rate (HR, bpm) was derived from the IBIs. Overall HRV was assessed by computing the standard deviation of normal-to-normal IBIs (SDNN, ms). The measure of short term, or high frequency, variability (index reflecting vagal activity) was calculated as the square root of the mean squared differences of successive heart period differences (RMSSD, ms).

In addition, resting systolic (SBP, mmHg) and diastolic (DBP, mmHg) blood pressure measurements (sitting position, 5 min rest) were obtained at the initial visit from a subset of participants (9 alcoholics and 12 controls) using an automatic sphygmomanometer.

2.5. Statistical analysis

Demographic and alcohol history measures, resting SBP and DBP, and subjective and objective sleep variables were compared with independent t-tests by group. Group differences in life time alcohol consumption, and days since the last drink were assessed with a non-parametric Mann Whitney U test.

Two main analyses were conducted. A 2 (Group: alcoholics and controls) × 3 (Stage: Wake, NREM, REM) mixed design ANOVA was applied separately to the mean value of each frequency-domain HRV index. For analysis of time-domain HRV variables, a 2 (Group: alcoholics and controls) × 6 (Hour: h1, h2, h3, h4, h4, h6) mixed design ANOVA was applied.

In addition, Spearman rank-order correlations were run between indices of severity of alcohol dependence and HRV frequency- and time-domain measures averaged across the whole night in alcoholics. In order to assess the relationship between subjective sleep quality and HRV indices irrespective of group (alcoholics and healthy controls), Spearman correlations were calculated between the self-reported PSQI scores and HRV frequency- and time-domain measures averaged across the whole night using the whole sample.

Fisher post hoc comparisons were performed on the significant effects and adjusted univariate Huynh-Feldt (H–F) tests for repeated measure were run when variables with more than 2 levels were involved. Due to a skewed distribution, the following variables were log transformed before statistical analyses: total power, HF_a, LF_a/HF_a ratio, SDNN, RMSSD.

For all statistical analyses, the probability level was set at $p < .05$ for significance.

3. Results

3.1. Demographic measures, resting blood pressure and alcohol history

Alcoholics compared to controls had elevated lifetime alcohol consumption ($p < .001$) and fewer years of education ($p < .001$). Groups did not differ in age, BMI, resting SBP and DBP, days since the last drink and consumption of beverages containing caffeine (see Table 1).

3.2. Self-reported sleep quality and PSG sleep parameters

Results of self-reported and objective sleep quality are provided in Table 2.

Alcoholics compared to controls had higher PSQI scores ($p < .001$) indicating a poorer self-reported sleep quality. Poor sleep quality in alcoholics was further confirmed by the objective PSG data. Alcoholics had a higher number of arousals ($p < .05$), percentage of N1 sleep ($p < .001$) and a reduced amount of N3 sleep ($p < .01$) than controls.

3.3. Frequency-domain HRV analysis of autonomic activity during stable sleep periods free from arousals

Mean and SD for the frequency-domain HRV variables obtained during stable sleep periods are provided in Table 3.

HR displayed significant main effects of group ($F_{1,28}=16.03$, $p < .001$) and sleep stage ($F_{2,56}=10.47$, $p < .001$), but the group by stage interaction effect was not significant. HR was higher in alcoholics compared to controls over the whole night, Post-hoc analysis revealed that in both groups, HR was lower in REM ($p < .05$) and NREM ($p < .001$) sleep compared to wake, and there was a trend for a higher HR in REM compared to NREM sleep ($p=.053$).

HF_a also displayed significant main effects of group ($F_{1,28}=5.70$, $p < .05$) and sleep stage ($F_{2,56}=21.10$, $p < .001$) but the group by stage interaction effect was not significant. Alcoholics had lower HF_a activity than controls. Post-hoc analysis revealed that in both groups, HF_a was higher in NREM sleep compared to REM sleep and Wake ($p < .001$), and was lower in REM sleep compared to Wake ($p < .05$).

LF_a/HF_a ratio did not display a significant group effect. There was, however, a significant stage main effect ($F_{2,56}=20.53$, $p < .001$) in the absence of a group by stage interaction effect. In both groups, LF_a/HF_a ratio was reduced in NREM sleep compared to REM sleep and Wake ($p < .001$).

Total power showed a tendency to be lower in alcoholics compared to controls ($p=.066$). There were no significant stage or interaction effects. No significant effects were found for **HF_p**.

3.4. Time-domain HRV analysis of autonomic activity across the night irrespective of the presence of arousals, awakenings, sleep stage composition or sleep stage transitions

HR displayed significant group ($F_{1,28}=13.87$, $p < .001$) and Time ($F_{5,140}=15.99$, $p < .001$) main effects, and a significant Group by Time interaction ($F_{5,140}=6.84$, $p < .01$). Post-hoc

analysis on the interaction indicated that in alcoholics compared to controls, HR was constantly higher during the first 4-hours of the night ($p < .05$) but did not differ from controls in the last two hours. HR dropped from h1 to h4 ($p < .05$), h1 to h5 ($p < .05$) and h1 to h6 ($p < .001$) in alcoholics and HR dropped from h2 to h4, h2 to h5 ($p < .05$) and h2 to h6 in controls ($p < .05$) (Fig. 1).

SDNN displayed significant Group ($F_{1,28}=4.67$, $p < .05$) and Time ($F_{5,140}=5.92$, $p < .001$) effects, but not Group by Time interaction. Alcoholics had lower SDNN (reduced HRV) compared to controls across the night. Post-hoc analysis indicated that SDNN increased (i.e. increased HRV) across hours of the night: from h1 to h4 ($p < .01$), h1 to h5 ($p < .01$) and h1 to h6 ($p < .001$); from h2 to h4 ($p < .05$) and h2 to h6 ($p < .001$); from h3 to h6 ($p < .01$) in both groups.

RMSSD displayed significant Group ($F_{1,28}=4.80$, $p < .05$) and Time ($F_{5,140}=2.97$, $p < .05$) main effects, and a significant Group by Time interaction ($F_{5,140}=2.88$, $p < .05$). Post-hoc analysis on the interaction indicated that RMSSD was significantly lower in the first four hours of the night but not in the next two hours of the night in alcoholics compared to controls ($p < .05$). RMSSD increased across the night: from h1 to h4 ($p < .05$) and h2 to h4 ($p < .05$), h2 to h5 ($p < .05$), h2 to h6 ($p < .001$); and from h3 to h6 ($p < .01$) (Fig. 3) in alcoholics but not in controls.

3.5. Relation between ANS activity and severity of alcohol dependence in alcoholics

There were no significant correlations between life time alcohol consumption or length of alcohol dependence and ANS measures (Table 4).

3.6. Controlling for potential confounding variables: exploratory analysis

Age and sex are known to impact on HRV (Jensen-Urstad et al., 1997) and even though groups were matched for age and sex, we re-ran all models presented above with either age or sex as a covariate or categorical predictor, respectively. Age did not interact with any of the levels of the models and all effects remained significant. Sex was not a significant predictor for any models.

Given that chronic nicotine exposure is associated with sympathetic hyper-activation (see Yun et al., 2005), to control for a potential effect of nicotine on autonomic activity we compared alcoholics smokers (N=7) and non-smokers (N=7) with non-parametric tests (Mann Whitney U) on frequency-domain HRV measures in each stage of sleep (Wake, NREM, REM) and on time-domain HRV measures in each hour of the night (h1, h2, h3, h4, h5, h6). No significant group differences were found.

3.7. Potential impact of reduced N3 in Alcoholics

Given the lower amount of N3 sleep in alcoholics compared to controls, we re-ran models from all analyses testing autonomic activity during artifact-free sleep periods considering N2 instead of NREM sleep. All the significant group main effects and interactions were maintained.

3.8. Associations between self-report sleep quality and nocturnal HRV measures

PSQI scores were positively associated with HR recorded during stable averaged sleep periods (Frequency-domain HRV analysis; r=.41, p <.05) as well as across the night irrespective of the presence of arousals, awakenings, sleep stage composition or sleep stage transitions (Time-domain HRV analysis; r=.42, p <.05) in the whole sample (N=30). No significant correlations were found between PSQI scores and other autonomic indices.

1. Discussion

This study used time and frequency domain analyses of HRV during sleep to investigate cardiac functioning and basal autonomic control in recently detoxified alcohol-dependent men and women compared to healthy controls. Alcoholics demonstrated a substantially elevated HR and reduced overall HRV based on time- and frequency-domain measures, compared to controls. These results provide compelling evidence of poor CV functioning in recently abstaining alcoholics, even during undisturbed sleep. HR and HRV measures showed the greatest difference between alcoholics and controls in the first part of the night, with evidence of some recovery of ANS modulation of CV activity in alcoholics later in the night.

Findings of an overall higher heart rate, reduced HRV and lower high frequency measures in recently sober alcoholic men and women are consistent with two other studies that investigated these measures during sleep in men (Ganesha et al., 2013; Irwin et al., 2006) and with other studies that investigated HRV during wakefulness (Malpas et al., 1991; Pitala et al., 2000; Yokoyama et al., 1991). A possible mechanism for suppressing HRV in chronic alcoholism is neuropathy of the vagus nerve, which is common with alcohol dependence (Barter and Tanner, 1987; Duncan et al., 1980; Johnson and Robinson, 1988; Villalta et al., 1989) and has been confirmed by a post mortem study showing reduced density of myelinated fibers of the vagus nerve in chronic alcoholics compared to controls (Guo et al., 1987), suggesting permanent damage to vagal ANS functioning.

Despite this evidence supporting a poor vagal ANS functioning in alcoholism, in our experiment we cannot completely confirm abnormal vagal modulation in recently sober alcoholic men and women. Our results of reduced HF variability in alcoholics could be partly explained by the overall reduced total HRV (showing a trend to be lower in alcoholics compared to controls in the frequency domain HRV analysis and significant in the time domain HRV analysis), which would explain the non-significant variation in LF_a/HF_a ratio, as also found in previous studies (Ganesha et al., 2013; Irwin et al., 2006). Without direct measures of vagal functioning, we cannot conclude that in alcoholics there is a selective reduction in vagal outflow and thus a specific fall in the HF component. However, even if not selective, the fall in the HF activity may still be due to a vagal factor mediating the overall drop in HRV.

The alcoholics in our study had been dependent for more than 3 years, with 78% of the sample being dependent for more than 10 years. They were studied between 1-6 weeks after their last drink and our findings, therefore, cannot be attributed to the known acute effects of alcohol (Johnson et al., 1986; Koskinen et al., 1994; Murata et al., 1994; Reed et al., 1999;

Sagawa et al., 2011; Weise et al., 1986) or acute alcohol withdrawal on the ANS (Bär et al., 2006). In agreement with Irwin et al. (2006), we did not find any correlations between night-time HRV measures and length of alcohol dependence or lifetime alcohol consumption in our sample of alcoholics. In contrast, previous studies have reported an association between severity of day-time ANS dysfunction and alcohol dependence (Monforte et al., 1995; Rechlin et al., 1996; Villalta et al., 1989).

Our inclusion of female subjects enabled a determination that alcohol dependence impacts the ANS during sleep to a similar extent in male and female alcoholics. We previously also showed that there are few sex differences in the impact of alcohol dependence on sleep architecture despite male alcoholics having greater lifetime alcohol consumption (Colrain et al., 2009).

The reduction in heart rate and increased HRV across the night in controls and alcoholics could be mediated by sleep. Sleep is tightly coupled to modulation of ANS activity. Sleep exerts a regulatory control over CV functions, which in turn influence sleep, resulting in a bidirectional relationship (Trinder et al., 2012). In healthy individuals, ANS control is characterized by increased vagal activity and reduced sympathovagal balance, increased baroreflex sensitivity, reduced sympathetic vascular tone and muscle sympathetic nerve activity during NREM compared to REM sleep and Wake (Trinder et al., 2012). Even though the alcoholics had less HF activity compared to controls in pre-sleep wakefulness, NREM and REM sleep, they still showed sleep-related modulation of HF power, which was highest in NREM sleep, as seen in controls. Alcoholics appeared to show a stronger sleep-related drop in HR and increase in RMSSD (a HF measure) across the night, such that these measures no longer differed significantly from controls by the end of the night. Similarly, Irwin et al. (2006) found that the group difference between alcoholics and controls in HF power was significant only during the first NREM/REM sleep period but not in successive periods. These findings suggest that sleep may help the ANS system recover to some extent. The changes in ANS measures across the night may also be mediated by the circadian system; heart rate and high frequency activity are under circadian regulation although, as indicated by the relatively small decline in heart rate across the night in controls, circadian regulation of the ANS is moderate compared to the impact of sleep. There is evidence from previous studies indicating an abnormal nocturnal melatonin secretion, in abstinent alcoholics (Kühlwein et al., 2003) with decreased levels of melatonin in alcoholics compared to controls only in the first part of the night. As melatonin secretion is known to affect ANS functioning (Nishiyama et al., 2001), a delay in the nocturnal rise of melatonin in alcoholic patients, is supportive of altered circadian rhythmicity. Finally, Armitage and colleagues (2012) recently suggested a lower nocturnal accumulation of delta EEG power in the first NREM period and a slower dissipation of delta power across the night (within consecutive NREM periods) during a 3-h sleep delay paradigm in abstinent alcoholics compared to healthy controls. Thus, we cannot exclude that an alteration of sleep homeostasis contributes to maintenance of high abnormal ANS functioning and a greater within night ANS activity reduction in alcoholics compared to controls.

Just as sleep could impact the ANS, it is also conceivable that poor autonomic functioning in the alcoholics could impact their sleep. For example, a pathway to insomnia is believed to be

mediated by a state of hyperarousal, given that insomniacs show increased heart rate and sympathetic dominance and reduced vagal activity during both day-time and night-time (Riemann et al., 2010). Our results show a significant positive correlation between perceived sleep quality (PSQI scores) and nocturnal heart rate measures in the combined group of alcoholics and controls, providing further support for the complex bidirectional relationship between sleep and autonomic functioning. Further studies are needed to determine whether the low HRV especially in the first half of the night may actively contribute to poor sleep in chronic alcoholics.

These results have to be considered in light of the limitations of this study. First, the sample size is relatively small, especially for the exploratory analysis of the impact of sex, age, and nicotine comorbidity. Also, given the small period of abstinence prior to study (less than a month since the last drink), it is possible that residual withdrawal symptoms or residual detoxification medication effects may still influence sleep and/or autonomic system function. Further research is needed to investigate the interactions between the ANS, sleep, and circadian system in recovering male and female alcoholics in a longitudinal study, from weeks to months after the beginning of abstinence. We also did not make measures of nerve conduction speed, which would be critical to confirm whether the lower HF power reflects reduced vagal tone in alcoholics. In addition, alcoholics had lower education than controls which could have contributed to the depressed HRV (Lampert et al., 2005), over and above the effect of alcohol-dependence. Finally, the level of CV fitness, known to impact HRV measures (Perini and Veicsteinas, 2003), was not investigated in this study. However, we controlled for potential confounding effects of age and gender on sleep and ANS functioning. In addition, considering the potential effect of nicotine consumption on ANS (Yun et al., 2005), we compared a sub-group of smokers vs. non-smokers within the alcoholics group and we did not find any group differences in the HRV measures.

In conclusion, we have found that recently sober alcoholic men and women have a substantially faster heart rate and reduced HRV across the night and within stages of NREM and REM sleep, indicating poor CV functioning, which likely contributes to their increased risk for CV disease (Tsuji et al., 1996).

We can speculate that the association between ANS and sleep measures together with the finding of some within-night “recovery” in ANS measures in alcoholics indicates a possible role of sleep in mediating this recovery, suggesting that treating sleep problems may not only reduce risk of relapse (Brower, 2003) but also may lead to improved CV functioning in alcoholics. A direct intervention focused on improving sleep quality in alcoholics is necessary to confirm this.

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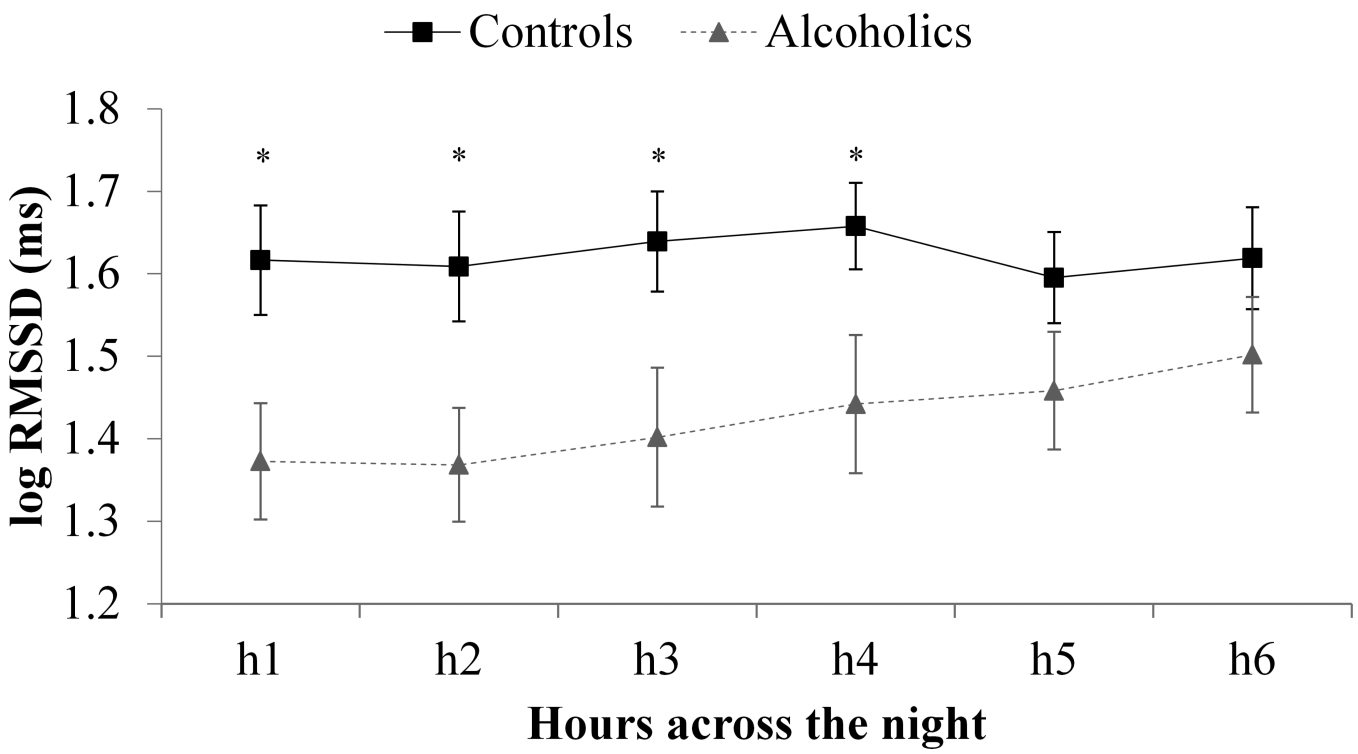

Fig. 1.

Means and standard errors for HR, derived from time-domain analysis, in recently-sober alcoholics and controls across hours of the night. Significant group differences (*, p <.05) are marked in the graph.

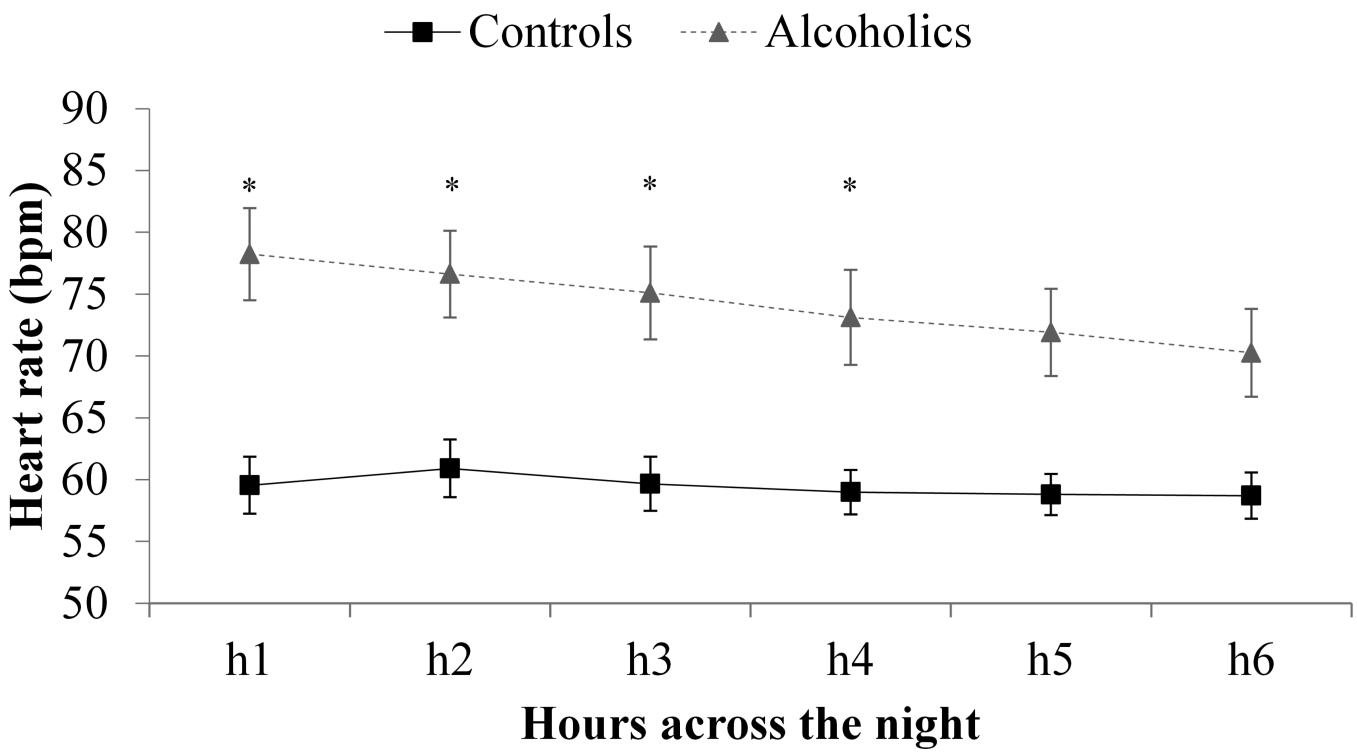

Fig. 2.

Means and standard errors for RMSSD, derived from time-domain HRV analysis across hours of the night, irrespective of awakenings, arousals, and sleep stages, in recently-sober alcoholics and controls. Significant group differences (*, p <.05) are marked in the graph.

Table 1

Demographics and alcohol history (mean +/− SD) for participant groups.

	Controls (No. 16)	Alcoholics (No. 14)	*t* or *z* values	
Male/Female (No.)	8/8	7/7	-	-
Age (y)	45.2 (9.1)	42.0 (9.0)	0.98	Ns
Caucasian (No.)	8	7	-	-
BMI (kg m-2)	24.5 (3.5)	24.9 (2.7)	−0.39	Ns
Education (y)	17.1 (1.8)	12.6 (2.2)	6.07	***
Length of dependence (y)	-	17.2 (9.7)	-	-
Lifetime alcohol use (Kg)	124.5 (226.8)	1215.8 (742.0)	−4.19[a]	***
Days since the last drink	16.3 (22.2)	19.8 (10.1)	−1.37[a]	Ns
Beverages containing caffeine (cups/day)	1.0 (1.1)	2.0 (2.1)	−1.61	Ns
Nicotine consumption (packets of cigarettes per year)	11.4 (45.6)[c]	247.7 (478.0)[d]	-	-
SBP (mmHg)[b]	120.1 (14.4)	122.7 (13.6)	0.17	Ns
DBP (mmHg)[b]	73.7 (8.5)	72.7 (12.3)	0.05	Ns

BMI, Body Mass Index; **SBP**, Systolic Blood Pressure; **DBP**, Diastolic Blood Pressure; **Ns**, not significant

*** $p < .001$

[a] Mann-Whitney U z value

[b] n = 9 alcoholics and 12 controls

[c] 1 smoker

[d] 8 smokers

Table 2

Self-reported sleep quality and sleep architecture variables derived from analysis of a night of clinical polysomnography in 16 alcoholics and 14 controls.

	Controls (No. 16)	Alcoholics (No. 14)	*t* value	
Self-reported sleep quality (PSQI score)	2.75 (2.54)	9.11 (4.89)	−4.55	***
TST (min)	395.4 (54.9)	401.8 (57.3)	−0.32	Ns
SOL (min)	11.2 (8.3)	10.2 (8.8)	0.33	Ns
ROL (min)	95.3 (19.1)	78.3 (52.1)	1.21	Ns
SE (%)	85.7 (6.5)	84.6 (8.7)	0.40	Ns
WASO (%)	11.9 (6.2)	13.3 (8.5)	−0.53	Ns
Time in N1 (% of TST)	7.6 (3.3)	12.9 (4.4)	−3.75	***
Time in N2 (% of TST)	48.6 (5.5)	45.3 (10.2)	1.11	Ns
Time in N3 (% of TST)	11.8 (5.7)	5.9 (4.4)	3.10	**
Time in REM (% of TST)	17.7 (6.7)	20.4 (6.6)	−1.11	Ns
Number of arousals (>3 s, < 15 s)	61.6 (25.1)	93.8 (41.3)	−2.62	*
Number of awakenings (> 15 s)	29.1 (9.8)	32.3 (13.6)	−0.73	Ns

REM, rapid-eye-movement; **PSQI**, Pittsburgh sleep quality index; **TST**, total sleep time; **SOL**, sleep onset latency; **ROL**, rem onset latency; **SE**, sleep efficiency; **WASO**, wake after sleep onset; **Ns**, not significant

* $p < .05$

** $p < .01$

*** $p < .001$.

Table 3

Mean and SD for the frequency-domain heart rate variability variables obtained during stable sleep periods in 16 alcoholics and 14 controls.

	Group	Wake	NREM	REM
HR (bpm)	Alcoholics	77.7 (13.0)	72.3 (13.1)	73.4 (12.1)
	Controls	60.2 (10.1)	57.78 (7.84)	60.0 (7.2)
Total Power (log ms^2)	Alcoholics	2.163 (0.448)	2.155 (0.457)	2.127 (0.474)
	Controls	2.470 (0.487)	2.474 (0.396)	2.348 (0.379)
HF_a (log arbitrary units)	Alcoholics	1.072 (0.404)	1.405 (0.491)	1.001 (0.445)
	Controls	1.549 (0.534)	1.761 (0.498)	1.294 (0.482)
LF_a/HF_a ratio	Alcoholics	0.350 (0.431)	−0.192 (0.470)	0.383 (0.470)
	Controls	0.118 (0.542)	−0.162 (0.342)	0.299 (0.392)
HF_p (Hz)	Alcoholics	0.263 (0.046)	0.250 (0.036)	0.249 (0.044)
	Controls	0.246 (0.044)	0.239 (0.044)	0.236 (0.035)

HF_a, absolute high frequency power; **HF_p**, HF peak frequency; **HR**, heart rate; **LF**, low frequency; **NREM**, non-rapid-eye-movement; **REM**, rapid-eye-movement

Table 4

Spearman's rank correlation coefficients between heart rate variability (HRV) frequency- and time-domain variables (averaged across the whole night) and severity of alcohol dependence in 14 alcoholic patients.

	HRV time-domain measures			HRV frequency-domain measures			
	HR (bpm)	**SDNN (ms)**	**RMSSD (ms)**	**HR (bpm)**	**HF_a (arbitrary units)**	**Total power (ms^2)**	**LF_a/HF_a ratio**
Lifetime alcohol use (Kg)	0.21	0.10	−0.02	0.20	−0.13	0.09	0.50
Length of dependence (y)	0.01	−0.22	−0.20	0.01	−0.30	−0.23	0.16

HF, high frequency; **HR**, heart rate; **LF**, low frequency; **RMSSD**, the square root of the mean squared differences of successive heart period differences; **SDNN**, standard deviation of normal-to-normal inter-beat-intervals.