Heart rate variability during sleep in detoxified alcohol-dependent males: A comparison with healthy controls

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ABSTRACT

Context: Alcohol dependence can lead to autonomic neuropathy resulting in increased cardiac morbidity and mortality. This has previously been evaluated using heart-rate variability.

Aims: We compared sleep heart-rate variability of alcohol-dependent patients with that of healthy controls in this study.

Settings and Design: This study was conducted at NIMHANS, Bangalore. A case control study design was adopted.

Materials and Methods: Sleep heart-rate variability of 20 male alcohol-dependent inpatients was recorded on the 5th day after detoxification. Sleep heart-rate variability was also recorded in 18 age- and gender-matched healthy controls.

Statistical Analysis: The groups were compared using t-test for continuous variables and Chi-squared test for discrete variables.

Results: Both time and frequency domain measures were significantly lower in the patients as compared to the controls, indicating decreased HRV in alcohol-dependent individuals.

Conclusions: Decreased HRV in alcohol dependence indicates potential autonomic neuropathy.

Key words: Alcohol dependence, autonomic neuropathy, cardiac morbidity, heart-rate variability, sleep electrocardiogram

INTRODUCTION

Alcohol and cardiac morbidity have a J-shaped relationship with each other. Previous studies have shown that those who never consume alcohol and those who consume it in large quantities have greater cardiac morbidity and mortality.[1] The mechanisms underlying the excessive cardiac morbidity and mortality among heavy alcohol users are relatively unexplored. It is known that chronic and heavy alcohol use has a toxic effect on the nervous system,[2] including effects on autonomic nervous system.[3] Specifically, heavy alcohol use can cause cardiac autonomic neuropathy,[4] which in turn, is associated with greater mortality.

Though many physiological factors affect cardiac functions like heart rate, the role of the autonomic nervous system is quite prominent. Resting cardiac autonomic function reportedly favors energy conservation by way of parasympathetic dominance over sympathetic influence. Heart rate is characterized by beat-to-beat variability over a wide range, which has been reported to indicate vagal dominance and thereby parasympathetic dominance.[5] Heart rate variability (HRV) is now an accepted term to describe both instantaneous heart rate and RR intervals. Studying HRV forms an important part of the diagnosis of autonomic neuropathy.[6] It has been studied as a non-conventional risk factor for cardiac mortality.[7,8] Lower variability in the heart rate has been consistently shown to be associated with greater cardiac mortality.[9,10] Low HRV is associated with increased risk of all-cause mortality, and low HRV has been proposed as a marker for disease.[11]

Alcohol use/dependence can affect HRV. HRV decreases immediately after alcohol consumption.[12] In those with
alcohol dependence, HRV is lower than in healthy individuals even after several days of abstinence. This decrement may improve with abstinence for long periods of time. A study of 24-h ambulatory HRV found significantly reduced HRV in alcohol-dependent men with established vagal neuropathy and in some without. Alcohol dependence has been shown to compromise vagal output measured before sleep onset, which correlates with loss of delta sleep and morning sleep impairments. Reduced HRV was found in alcohol-dependent patients with negative mood states and compulsive drinking. Rechlin et al. reported reductions in HRV in patients with alcohol dependence, and this has been consistently reported in subsequent studies. A recent study reported no differences in HRV between alcohol-dependent and nondependent groups. A recent meta-analysis reported a medium effect size for reduced HRV with alcohol dependence.

Most studies used HRV measures based on the ECG obtained during the daytime. HRV can change due to physical activity, emotional atmosphere, and even cues related to alcohol. HRV measured during sleep is likely to overcome the effects of these confounds. Sleep ECG has been posited to be a reflection of natural background HRV. Physical and psychiatric disorders can confound HRV studies in alcohol dependence and also need to be accounted for. We compared sleep HRV of patients with alcohol dependence with that of healthy controls in this study.

MATERIALS AND METHODS

Inpatients from the Deaddiction Center, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, with a diagnosis of alcohol dependence syndrome (ADS) (ICD 10), were recruited for this study. Subjects (n=20) aged between 20 and 60 years were recruited after obtaining written informed consent. Age- and gender-matched healthy controls (n=18) without personal and family history of alcohol use were recruited from among volunteers.

The Deaddiction Centre Questionnaire (DCQ) was used to assess the patients for alcohol dependence on the day of admission. The DCQ contains questions from the Semi-structured Assessment for the Genetics of Alcoholism (SSAGA II) and can generate an ICD-10 and DSM-IV diagnoses of ADS. It also provides other details, including age at onset of drinking, age of regular use of alcohol, quantity, and frequency of alcohol use, medical complications of ADS, and information on nicotine and other substance use. There was no other psychiatric co-morbidity as it was confirmed independently by two clinicians. A detailed physical examination including a neurological examination was done for all subjects to rule out peripheral neuropathy. Laboratory investigations, including electrocardiogram (ECG), blood sugar levels, liver function tests, renal function tests, and serum electrolytes were done for all patients as a routine evaluation. These revealed no evidence of cardiovascular disorders or diabetes in subjects.

The patients were detoxified using a front-loading regimen of diazepam. Detoxification was completed within 48 hours of admission, followed by a drug wash-out period of 5 half-lives. At the time of ECG acquisition, the patients were not on any medications that could alter HRV. They did not have any signs of alcohol withdrawal, as determined by the questions for alcohol withdrawal in the DCQ.

The controls were screened clinically for the presence of any psychiatric disorders, including any substance use disorder. Six of the controls had history of cigarette smoking with an average use of 2 cigarettes/day over the past 6 months. They had not consumed alcohol for at least 2 weeks prior to the ECG acquisition.

ECG acquisition

Sleep ECG was recorded on the 8th day of admission in the subjects. It was recorded from 10 PM to 6 AM in both subjects and controls. NIVIQURE Ambulatory ECG (Technonivilac, Bangalore, India; 2 channel, 10 bit, 1024 sampling rate), a portable ECG instrument, was used to record the sleep ECG in lead-I electrode position. The instrument was programmed using NIVIQURE software to record ECG in epochs of 5-min duration at intervals of 1 hour. The data recorded was then transferred to a computer for offline analysis using the NIVIQURE software. The variables studied are summarized in Table 1. For each individual, eight such epochs were recorded. For the purpose of analysis, the first and the last epochs were excluded as there was a possibility of the participants being awake during these periods. Of the remaining six, five artifact-free epochs were analyzed.

HRV parameters

Both time and frequency domain measures were analyzed.

The time domain measures included (1) NN50: Count of number of pairs of normal to normal RR (NN) intervals differing by >50 ms, (2) standard deviation of NN intervals for period of interest, measured in milliseconds (SDNN), (3) root mean square of successive differences of NN intervals for a period of interest, measured in milliseconds (rMSSD), (4) pNN50: Percent of NN intervals >50 ms different from previous (NN) for period of interest.

Frequency domain measures included (1) total power over the measured period (TP), (2) very low frequency measures rhythms between every 25 s and every 5 min (0.0033–0.04 Hz) (VLF), (3) low frequency measures HR rhythms from 2.5 to 9 cycles/min (0.04-0.15 Hz) averaged over 5 min (LF), (4) high frequency captures variations in HR due to respiratory sinus arrhythmia at 9 to 24 cycles/min (0.15-0.4 Hz) (HF), and (5) LF/HF ratio.
Statistical analysis
Statistical analysis was performed using the Statistical Package for Social Sciences (version 11.0). The analyses were conducted separately for each epoch and for the average measure of all the epochs for each variable. The groups were compared using t-test for continuous variables and Chi-squared test for discrete variables. Cumulative exposure to alcohol was calculated using the formula, average units of alcohol per day X number of years of regular use X 365. Pearson’s correlation coefficient was used to evaluate the correlations between average HRV measures on one hand and age and cumulative exposure to alcohol on the other. Statistical significance was fixed at P<0.05.

RESULTS
There was no statistically significant difference between the mean ages of patients (38.8) and controls (39.7) (t=0.241, P=0.811). The patients consumed a mean (SD) of 8.32 (6.43) units of alcohol per day for a mean (SD) of 12.8 (8.6) years. None of the subjects or controls had any ECG abnormalities or elevated blood sugar levels.

Patients had significantly lower SDNN, RMSSD, and pNN50; they also had lower LF, HF, and total power [Tables 1 and 2]. They did not differ in VLF and LF/HF ratio. Average total power correlated inversely with cumulative exposure to alcohol (number of units per typical day X drinking days per year) (Pearson’s correlation coefficient (r)=-0.452; P=0.046). It also had inverse correlation with age only in the control group (r=-0.542; P=0.02) and not in the subjects (r=0.005; \(P=0.985\)). Significantly greater proportion of the subjects (n=14; 73.7%) used tobacco than the controls (n=4; 23.5%; Chi-square=9.03; P=0.003).

DISCUSSION
In our study, patients with alcohol dependence were found to have lower HRV during sleep than age-and gender-matched healthy controls. This was found in both time- and frequency-domain measures and is consistent with the results of earlier studies using daytime\(^{[13]}\) and 24-hour\(^{[17]}\) HRV measurements. None of the patients had any comorbidities like diabetes\(^{[30]}\) or depression\(^{[31,32]}\) that could have influenced HRV.

rMSSD and pNN50 are time domain measures that reflect the vagal tone in subjects with normal sinus rhythm.\(^{[28]}\) The lower values on these measures in alcohol-dependent patients could indicate lower parasympathetic activity in these individuals as compared to healthy controls. Respiratory rate is an important physiological parameter of the periodic components of HRV and the HF can capture variations in HRV due to respiratory sinus arrhythmia.\(^{[28]}\)

| Parameters | Units | Description | Implication |
|------------|-------|-------------|-------------|
| Time domain measures |
| SDNN       | ms    | Standard deviation of all NN intervals | Reflects the total HRV |
| RMSSD      | ms    | The square root of the mean of the sum of squares of differences between adjacent NN intervals | Reflects vagal activity with normal sinus rhythm |
| NN50       | Count | Count of number of pairs of NN (Normal to normal RR) intervals differing by >50 ms | |
| pNN50      | Percent | NN50 divided by total number of all NN intervals | Reflects vagal activity with normal sinus rhythm |
| Frequency domain measures |
| Total power | ms\(^2\) | 0.04-0.4 Hz | Reflects total HRV |
| Very low frequency power | ms\(^2\) | 0.003-0.04 Hz | Reflects vagal effects on HRV |
| Low frequency power | ms\(^2\) | 0.04-0.15 Hz | Both sympathetic and parasympathetic |
| High frequency power | ms\(^2\) | 0.15-0.4 Hz | Reflects vagal activity |
| LF/HF Ratio | | | Sympathetic-parasympathetic balance |

| Variable | Patients** | Controls** | t  | P  |
|----------|------------|------------|----|----|
| Time domain variables |
| SDNN     | 76.6 (19.4) | 96.8 (24.2) | 2.85 | 0.007 |
| RMSSD    | 23.7 (10.9) | 34.5 (9.1)  | 3.17 | 0.003 |
| NN50     | 2.8 (4.2)   | 6.6 (4.0)   | 2.79 | 0.009 |
| Frequency domain variables |
| VLF      | 111.8 (21.2) | 105.5 (21.7) | 0.900 | 0.374 |
| LF       | 141.0 (30.5) | 194.8 (44.8) | 4.366 | <0.001 |
| HF       | 113.1 (60.2) | 162.1 (79.4) | 2.156 | 0.038 |
| Total power | 365.9 (74.7) | 462.4 (92.4) | 3.556 | 0.001 |
| LF/HF    | 2.0 (0.8)   | 2.0 (0.8)   | 0.082 | 0.935 |

*Three of the subjects had RMSSD and PNN50 values beyond ±3 SD of the mean; They were excluded from the analysis of these variables; **The figures are in mean (SD); VLF – Very low frequency; LF – Low frequency; HF – High frequency
Lower HF in the absence of any respiratory abnormalities in the study group, again indicates reduced vagal tone in the alcohol-dependent group as compared to controls. LF/HF ratio, which reflects the balance between the sympathetic and parasympathetic systems, was not different between the groups. It could be a function of both LF and HF being lower in the study group as compared to controls.

There was a significant negative relationship between the cumulative exposure to alcohol and the HRV measures. Persons who had the greatest exposure to alcohol (quantity × frequency) had the lowest scores on both time- and frequency-domain measures of HRV.

These observations collectively appear to implicate chronic heavy alcohol use as a causal agent in the diminution of the variability in HRV. This would suggest that chronic alcohol dependence is, by itself, an independent risk factor for increased cardiac morbidity.

None of the patients had clinically detectable peripheral neuropathy. An earlier study reported subtle signs of autonomic neuropathy by 24-h ambulatory HRV monitoring even without clinically recognizable neuropathy. HRV is found to increase during sleep because the arrhythmias decreased during orthodox slow wave sleep confer some extra stability on the sinoatrial axis. We recorded sleep HRV as it is likely to be sensitive to subtle autonomic neuropathy much before it is apparent clinically and it could be a harbinger of future cardiac morbidity in these patients.

This study has some merits. We assessed HRV using sleep ECG. This avoided confounds like physical activity, emotional disturbances, and cues to alcohol, which may influence HRV. We used age-matched controls and thereby avoided the influence of age on the interpretation of the differences in HRV. Indeed, in our sample, we observed an inverse correlation between age and total power. This was seen only in the control group. This is conceivably because, in the patient group, the effect of age on HRV was masked by the overwhelming influence of alcohol on the HRV. The effect of alcohol withdrawal on HRV was avoided by acquiring the ECG after detoxification was complete, thereby ensuring that there were no withdrawal symptoms.

The study has some limitations. Firstly, we did not obtain a polysomnograph record of the electroencephalogram to correlate with the ECG epochs in order to determine the stage of sleep during which the ECG was recorded. There is significant autonomic arousal during the rapid-eye-movement period (REM) sleep, and HRV measured during this stage may be lower than the ones measured during other stages. However, we obtained five epochs of ECG recordings interspersed through the entire sleep period using the same frequency in both patients and alcoholics. Patients tended to have lower HRV uniformly across all epochs and all HRV measures than controls. This indicates that the difference between the groups in HRV is unlikely to be due to influence of the different stages of sleep. Second, the ECG of controls was obtained in their homes, whereas that of patients was obtained in the hospital. This could have influenced the quality of sleep, although none of the subjects complained of poor sleep on the days of ECG acquisition. Third, significantly greater proportion of patients used tobacco. We avoided the acute effects of tobacco use on HRV by recording the ECG throughout the night. The small number of subjects in the study precluded a separate comparison of non-tobacco users in the two groups. However, an earlier study using day-time ECG recording had shown that alcohol-dependent subjects had lower HRV than healthy controls though both had similar rates of tobacco use. This further suggests that lower HRV in these patients is likely to be only due to chronic alcohol use. Fourth, withdrawal symptoms such as sweating, anxiety, increased systolic and diastolic blood pressure, and poor sleep, indicative of increased sympathetic nervous system activity, a physiological state associated with reductions in HRV, were not reported by any of the subjects during ECG acquisition. However, not using a scale to measure withdrawal could be considered a limitation of this study.

To conclude, sleep HRV appears to be a marker for potential autonomic neuropathy and related cardiac morbidity in individuals with alcohol dependence. Further studies in this population are required to recommend its use in routine clinical practice.

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