NIMHANS JOURNAL, 15(3), July 1997, pp 219–223

Subclinical Autonomic Neuropathy in Alcoholics: Decreased Heart Rate Variability

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Cardiac autonomic neuropathy is known to occur in alcoholics but the extent of its subclinical form is not usually recognized. Heart Rate Variability (HRV) analysis can detect subclinical autonomic neuropathy. In this study the HRV parameters were compared in 20 neurologically asymptomatic alcoholics, 20 age-matched normals and 16 depressives. All were males. ECG was recorded in a quiet room for four minutes in supine position. Time and Frequency domain parameters of HRV were computed by a researcher blind to clinical details. Alcoholics had significantly smaller Coefficient of Variation of R-R intervals (CV_{R-R}) on time domain analysis and smaller HF band (0.15-0.5 Hz) power on spectral analysis. The decreased Heart Rate Variability indicates cardiac autonomic dysfunction.

Key words - *Heart rate variability, Alcoholics, Autonomic neuropathy.*

Alcoholism causes neurotoxic effects and autonomic neuropathy is one of them. Cardiac autonomic neuropathy may go unnoticed and is not usually detected in routine clinical practice. Subclinical forms of cardiac autonomic dysfunction merit assessment. Autonomic nervous system influences cardiac function. Cholinergic outflow from the vagus (parasympathetic) decreases and adrenergic outflow from the sympathetic system increases the heart rate. It has been shown that heart rate is not always constant contrary to what is found by clinical examination. There is a variation in the rate which is measurable only by advanced computer aided procedures. Such procedures yield several measures of heart rate variability (HRV) which are sensitive to even minor but selective perturbations in either sympathetic or parasympathetic systems[1]. Autonomic neuropathy in diabetics is detected early using HRV analysis when other clinical evidence of neuropathy was lacking[2].

HRV analysis has detected subclinical autonomic neuropathy in alcoholics[3,4] too. HRV parameters in a proportion of alcoholics improve after sufficient period of abstinence[5], suggesting indirectly an association between chronic alcohol exposure and autonomic neuropathy. Alcoholism may itself be symptomatic of depression. The latter too is associated with changes

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in HRV[6]. Therefore, undetected depression in alcoholics can confound HRV parameters. Hence inclusion of yet another control group with depressive disease is warranted in studies examining HRV in alcoholics. Being a noninvasive technique, HRV analysis holds promise in routine clinical practice for screening the alcoholic patients for evidence of autonomic neuropathy. This study was designed to examine cardiac autonomic function using the HRV parameters in neurologically asymptomatic nondepressed alcoholics.

Methods

Sample : Twenty male inpatients in the deaddiction ward of NIMHANS hospital formed the sample of this study. They met the ICD-10 criteria[7] of alcohol dependence but without history of any other drug use. They were free from psychiatric and neurological disorders. None had evidence of diabetes or exposure to heavy metals or solvents occupationally. The ECG recording was done two weeks after the last drink. At the time of the recording they were free from withdrawal symptoms and were off psychotropic and other drugs for atleast 48 hours (2-7 days) except vitamin supplements. Twenty age-matched male volunteers without any substance dependence or harmful use or any psychiatric morbidity formed one control group. None had used alcohol in the past 15 days. A group of 16 male treatment-naive depressives meeting ICD-10 criteria[7] of depressive episode formed another control group. None of the depressives was psychotic or bipolar and none had history of alcohol or drug abuse. Twelve each of alcoholics and normals and ten of the depressives were also smokers but did not smoke within two hours before recording. All the subjects underwent detailed medical evaluation to rule out any cardiac (arrhythmia, ischemic heart, hypertension, valvular disease), respiratory (asthma, chronic obstructive pulmonary disease) or neurological disorder (including autonomic neuropathy). Blood pressure was recorded in supine and on immediate standing postures. None of the subjects had evidence of postural hypotension. A 12-lead paper ECG was normal in all alcoholic subjects. All subjects gave informed consent.

ECG Recording

Recording was done in a quiet room always in the afternoon between 2.00 and 4.00 p.m. after lunch. After the application of the chest leads, the subjects were allowed to acclimatize to the room in supine position for 15 minutes before ECG recording. ECG was recorded using a commercial ECG monitor. ECG signal of four consecutive minutes was digitized at 500 Hz using a 12 bit ADC and was stored in a personal computer and the data was analyzed without the knowledge of clinical details.

HRV Analysis

A. *Time Domain Analysis* : ECG was replayed on the computer screen to check for artefacts before analysis. The R waves were detected and from the resulting R-R interval series, the following time domain parameters were computed : the Mean Heart Rate (MHR), the Coefficient of Variation of R-R intervals (CV_{R-R} - ratio of the standard deviation of the R-R intervals to the mean), the Root Mean Square Successive Difference of intervals (the square root of the mean of the squared differences between adjacent RR intervals, RMSSD), the percentage of successive R-R intervals with a difference of greater than 50 msec (pNN50), the dif-

ference between the maximum (E) and the minimum (I) R-R interval (E-I) and the ratio of maximum to minimum R-R interval (E/I).

B. *Frequency Domain Analysis*: The instantaneous heart rate time series was obtained from the R-R intervals. Linear interpolation[8] was applied on the HR time series to obtain heart rate samples evenly spaced at 0.25 sec. From this interpolated time series the mean was removed and then using FFT, the power spectrum was obtained. The absolute power (BPM^2/Hz) in the very low frequency band (VLF, 0.01 - 0.05 Hz), the low frequency band (LF, 0.05 - 0.15 Hz) and the high frequency band (HF, 0.15-0.5 Hz), the total power in the frequency interval of 0.01 to 0.5 Hz and the ratio of HF to LF power (HF/LF) were calculated.

Statistics

Statistical Package for Social Scientists, Release 6 (SPSS Inc, 1993) was used for the analysis of the computer parameters. Age, Time and Frequency domain HRV parameters were compared between the groups using one-way ANOVA. The spectral power was log-transformed for the purposes of parametric analysis. Analysis of covariance (ANCOVA) with heart rate as the covariate was also used to compare the mean CV_{R-R} of the three groups.

Results

The three groups were comparable on age (Table I). The groups differed significantly on MHR, CV_{R-R}, RMSSD and pNN50. Alcoholics had smallest values of CV_{R-R}, RMSSD and pNN50, and highest MHR (Table I). Using analysis of covariance, the difference between the groups on CV_{R-R} was also examined, with MHR as covariate. The three groups continued to be different with alcoholics having smallest CV_{R-R} (DF=2,52, F=3.35, p=0.05). Alcoholics had lowest values in all frequency domain parameters but this reached significance only on HF (Table II). Even log transformed data showed similar differences on one-way ANOVA.

Table I
Mean (SD) age and time domain HRV Parameters

Variable	Alcoholics (n=20)	Normals (n=20)	Depressives (n=16)	Significance
Age in years	38.8 (7.2)	37.7 (8.2)	33.6 (7.8)	F=2.18 p=0.12
MHR in Beats/min	83.3 (10.6)	73.8 (9.8)	82.1 (17.2)	F=3.31 p=0.04
CV_{R-R}	2.9 (1.2)	4.4 (1.8)	4.2 (1.9)	F=4.76 p=0.013
RMSSD	17.3 (9.6)	30.3 (15.6)	31.1 (20.2)	F=4.91 p=0.011
pNN50	1.3 (2.3)	10.9 (12.9)	12.5 (15.7)	F=5.25 p=0.008
E-I in msecs	157.0 (112.3)	220.3 (107.1)	233.9 (142.9)	F=2.20 p=0.12
E/I	1.2 (0.23)	1.3 (0.15)	1.4 (0.27)	F=1.35 p=0.27

Oneway ANOVA, D.F. = 2,53

Table II
Mean (SD) frequency domain HRV parameters

Variable	Alcoholics (n=20)	Normals (n=20)	Depressives (n=16)	Significance**
HF Power* 0.15-0.5 Hz	425.1 (375.1)	1128.4 (1042.3)	1441.0 (1856.8)	F=3.53 p=0.036
LF Power* 0.05-0.15 Hz	567.6 (515.2)	1202.9 (963.4)	1226.5 (1315.5)	F=2.92 p=0.06
VLF Power* 0.01-0.05 Hz	1321.1 (1224.7)	1675.3 (1388.4)	1973.3 (2255.3)	F=0.72 p=0.49
H/L Ratio	0.96 (0.84)	1.16 (0.79)	1.21 (1.1)	F=0.42 p=0.66
Total Power 0.01-0.5 Hz	2313.9 (1903.5)	4006.6 (2761.1)	4640.7 (5269.3)	F=2.26 p=0.12

*BPM^2/Hz, **Oneway ANOVA, D.F. = 2, 53.

Discussion

In the study, alcoholics were different from normals and depressives on several HRV parameters. This is remarkable in that the alcoholics were free from most of the factors known to confound such a comparison. At the time of recording, all alcoholics were benzodiazepine-free for varying periods from two to seven days and their last alcohol drink was two weeks ago. None had other drug abuse disorder. They were free from psychiatric illness and neurological complications. None had evidence of diabetes or history of occupational exposure to heavy metals or solvents. All subjects were tested at the same time of the day to control for the circadian variation of HRV[9]. It is arguable that the HRV abnormalities observed in alcoholics might be related to an underlying psychiatric condition, for example depression, and not due to neurotoxic effects of alcohol. This possibility was excluded by recruiting alcoholics who were not clinically depressed.

The study confirmed earlier reports that alcoholics have smaller HRV parameters on both time and frequency domains[3,4]. Weise *et al.*[3] examined one of the measures of HRV - 'Mean Momentary Arrhythmia' (MMA-mean difference of successive RR intervals)- in alcoholics at different points of time during detoxification. The authors found that increases in heart rate in the first five days of withdrawal contribute to lower HRV measures and hence suggest that the testing be done atleast one week after last alcohol drink. In our sample, the alcoholics had higher MHR suggesting occult withdrawal state, although the testing was done two weeks after the last drink. Accordingly, we applied ANCOVA with MHR as the covariate and still the alcoholics had smallest $CV_{R\text{-}R}$, suggesting that in our alcoholic group merely increased MHR did not contribute to smaller HRV. The reduced $CV_{R\text{-}R}$ reflects decreased parasympathetic tone. The high MHR could also be an effect of lowered parasympathetic tone. The groups differed on RMSSD and pNN50, with alcoholics having lowest values suggesting reduced parasympathetic tone. Weise *et al.*[4] observed that acute consumption of alcohol lowers these HRV parameters. In the same study the authors also found that chronic alcoholics are different from controls in the HRV parameters but the testing was done in alcoholics whose last drink was only eight hours ago. In contrast, we have tested the subjects fifteen days after their last drink and this was ensured by studying only inpatient population. The HF band spectral power also reflects parasympathetic tone. The latter is more vulnerable to neurotoxic effects. In the present study the power in HF band was lower in alcoholics than other groups suggesting decreased parasympathetic activity.

The procedure of HRV estimation is based on a computer algorithm. Computation facilities, admittedly have not reached all clinical centers. With this limitation, HRV analysis is recommended in advanced centers only as an addition, but not to replace routine clinical tests of autonomic dysfunction. It is not possible to offer 'normal' values of HRV parameters with this small data. Fourteen (70%) alcoholics and (30%) of normal controls had smaller than median values (of the 40 subjects including alcoholics and controls) on following parameters: $CV_{R\text{-}R}$, RMSSD, pNN50 and HF power. However, a $CV_{R\text{-}R}$ of 2.5 or smaller detected 50% of alcoholics and only 10% each of normal and depressives as 'abnormal'. More work is needed to generate normal ranges to diagnose autonomic dysfunction using HRV analysis.

Acknowledgement

This research was supported by Medical Education and Research Trust grants 1995-96, Karnataka.

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