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The time-course of electrocardiographic interbeat interval dynamics in alcoholic subjects after short-term abstinence

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Abstract

Alcohol dependence has been correlated with decreases in heart rate variability. However, the time course of recovery of heart rate variability after cessation of alcohol consumption is unknown. We used electrocardiogram (ECG) data serially obtained from a population of detoxifying alcoholic subjects to determine the Hurst exponent of the ECG interbeat interval time series. Higher values of the Hurst exponent are associated with decreased heart rate variability when $H \leq 0.5$. We tested a series of response-surface models relating the Hurst exponent (H) thus obtained to the following independent variables: the time interval T (days since last use of alcohol), A (age in years at time of admission), and gender. The best-fit model was: $H(T) = (KA + H_m T + H_f T)/(1 + T)$, $F = 5.2$, $P(F) \leq 0.01$. Model parameters were: $K = 0.008 \pm 0.002$ (mean $\pm$ SEM); asymptotic H-values for males and females: $H_m = 0.24 \pm 0.02$ and $H_f = 0.16 \pm 0.03$, respectively, significantly different at $P \leq 0.05$. Age was the strongest predictor of initial H-values in this alcoholic population sample. © 2001 Published by Elsevier Science B.V.

Keywords: Heart rate; Electrocardiography; Alcohol-related disorders; Fractal; Toxicology

1. Introduction

Chronic excessive alcohol consumption is known to alter cardiac rhythm regulation, resulting in decreases in heart rate variability (Malpas et al., 1991; Rechlin et al., 1996). However, the effects of short-term abstinence on heart rate variability after long-term alcohol dependence are not well-defined. Previous works confirm that chronic excessive alcohol use is associated with decreased heart rate variability when measured up to 48 h from the last use of alcohol (Murata et al., 1994; DePetrillo et al., 1999a). The magnitude of respiratory sinus arrythmia was found to be correlated with other measures of heart rate variability (Laude et al., 1995) and decreased in alcoholic subjects after 1 week of abstinence when compared to nonalcoholic subjects (Hirsch et al., 1993).

We previously used a technique to measure the internal dynamics of an interbeat interval time series by calculating the Hurst exponent (H) as an index of heart rate variability (Hurst, 1951; DePetrillo et al., 1999b). This method has been shown to have utility in examining the pharmacodynamic effects of ketamine and ondansetron on ECG time-series (DePetrillo et al., 2000). Since decreases in heart rate variability are associated with higher values of H (Yamamoto et al., 1995), we hypothesized that in subjects admitted for alcohol detoxification, serially measured H values would decrease with increasing abstinence time, corresponding to recovery of cardiac rhythm regulation. We also performed frequency-domain analyses on the experimentally derived IBI time series for the purpose of comparing them with the nonlinear analysis.

2. Materials and methods

2.1. Subjects

The study was approved by the Institutional Review Board at the National Institute on Alcohol Abuse and Alcoholism. Subjects were evaluated using the Structured Clinical Interview for DSM-III-r (SCID) (Spitzer et al., 1990). The study group, 4 females and 16 male, included 15 Caucasians, 4 African-Americans, and 1 subcontinental

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Asian. Severity of alcohol dependence was estimated using the Michigan Alcoholism Screening Test (Selzer, 1971) as well as a time line follow-back method quantitating lifetime alcohol use (Wynn, 2000).

In Table 1, heavy alcohol use is defined by periods of time where the subject would imbibe at least 5 drinks per drinking episode at least twice per week (Eckardt et al., 1978). Frequency of use and quantity parameters were defined as cumulative number of days where any alcohol was consumed and mean grams of alcohol consumed per day, respectively, for the 6-month period immediately preceding admission for detoxification.

2.2. Data collection

Subjects were tested at least 24 h after the last dose of diazepam, and none exhibited Clinical Institute Withdrawal Assessment-Alcohol revised (Sullivan et al., 1989) scores >10 at the time of testing. All recording took place between 9:00 a.m. and 1:00 p.m. $Ag/AgCl_2$ gel electrodes were placed across the chest wall just above the nipple line, separated by 6 cm. Subjects remained supine and motionless while approximately 5 min of ECG data was recorded with eyes open. Testing was repeated weekly until discharge. An MM Polar XR transmitter in communication with a Mini-Logger Series 2000 receiver (Mini-Mitter, SunRiver, OR, USA) was used to sense and transmit the interbeat interval data at a sampling rate of 500 Hz, resulting in a timing accuracy of ± 1 ms (Ruha et al., 1997).

2.3. Extraction of interbeat interval values and determination of the Hurst exponent

The stored data were extracted using the Mini-Logger software Version 3.21 to an IBM 433Dx/Dp PC running MSDOS 6.22. The interbeat intervals were manually checked for anomalies. Corrections were made only if the irregular interval differed from the mean by a factor of 2 or greater, since many of the abnormal magnitudes represented a failure of the device to trigger based on R-wave sensing. This resulted in signal magnitudes that were approximately twice that of the preceding data points. Abnormal beat-to-beat intervals were corrected by removing the abnormal beats, depending on the situation. At most, 5% of the data required this filtering procedure. Filtered interbeat interval data was analyzed as previously reported (DePetrillo et al., 1999b). The filtering and analysis procedures were undertaken in blind fashion. Software used for computation of Hurst values can be obtained at ftp://helix.nih.gov/pbdp/Hsoftware/.

Frequency-domain analysis of experimentally derived IBI time series was undertaken using the Time-Series Statistical Analysis System, TSAS 3.01.01b (TSAS) compiled and run on a DEC 3000/600S AXP. Low-frequency power (LF) was computed between 0.00 and 0.15 Hz and high-frequency power (HF) between 0.15 and 0.5 Hz. The

Table 1
Demographic variables of study population

Variable	Values	SEM	Range
Age (years)	41.4	1.0	23–64
Years of heavy alcohol use	15.1	2.4	2–40
Frequency of use (days/6 months prior)	154.3	9.8	55–183
Quantity (g/day) over 6 months prior	222.7	31.8	30–588
Lifetime alcohol use (kg)	756.3	166.7	147–2693
Michigan Alcohol Screening Test score	42.6	3.2	23–59
Time interval from last use of alcohol (days)	6.3	2.1	0–32

Table 2
Exploratory analyses for demographic variables and outcome variables

	Spearman rho	*P*-value
MAST vs. age	−0.188	≥ 0.49
MAST vs. *H* (week 1)	0.204	≥ 0.49
Years of heavy alcohol use vs. *H* (week 1)	0.324	≥ 0.20
Frequency of use (days/6 months prior) vs. *H* (week 1)	0.312	≥ 0.21
Quantity (gm/day) over 6 months prior vs. *H* (week 1)	−0.15	≥ 0.68
Lifetime alcohol use (kg) vs. *H* (week 1)	−0.009	≥ 0.97
Mean IBI vs. *H* (week 1)	−0.202	≥ 0.40

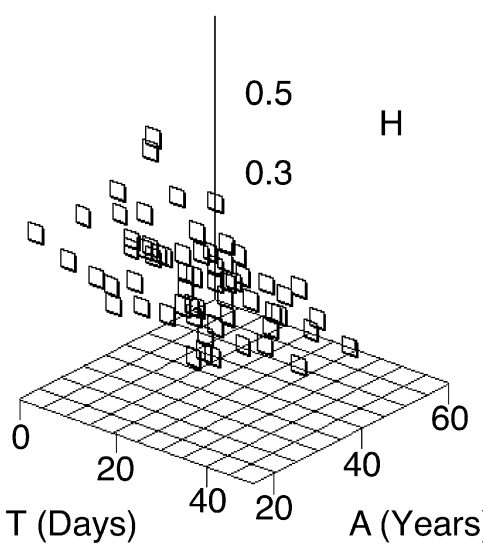

Fig. 1. Response surface showing the dependence of *H*-values on age (A, years) and time from last alcohol use (*T*, days).

Table 3
Model parameters and associated P-values

	Model I (male)		Model I (female)		Model II		Model III	
	F	Prob *F*	*F*	Prob *F*	*F*	Prob *F*	*F*	Prob *F*
Model Fit	4.47	0.03984	0.48	0.49945	5.18	0.00843	7.93	0.00016
		P-value		*P*-value		*P*-value		*P*-value
K	0.008	0.00003	0.008	0.12778	0.008	0.00001	0.007	0.00001
H_m	0.244	0.00010			0.244	0.00001	0.048	0.35920
H_f			0.162	0.00061	0.161	0.00001	−0.002	0.52451
P							0.111	0.20762
Number of parameters	2		2		3		4	

parasympathetic index (PNS) was computed as (HF/total power) and the sympathetic index (SNS) as (LF/HF). The same software package was used to generate time series using a spectral synthesis method with a $1/f$ noise distribution and defined means and standard deviations for purposes of comparing stability of parameters obtained from nonlinear and frequency-domain analyses.

2.4. Statistical analyses

The initial analysis consisted of plotting the data using a three-dimensional scatter plot with the x, y, and z axes being represented by age (A, years.), time from last use of alcohol (T, days), and H, respectively, thus constituting a response surface. A series of asymptotic equations describing the model response surface were tested, relating H to age and T. Age was chosen as an explanatory variable based on preliminary analysis of results relating age to H. The family of chosen functions were asymptotic since $H \geq 0$. Both asymptotic sigmoid and exponential decay models were examined, the latter of the form: $H(T) = KA(e^{-BT}) + H$.

Of the sigmoid models evaluated, three are shown below.

$$H(T) = \frac{KA + HT}{(1 + T)}. \quad \text{(Model I)}$$

$$H(T) = \frac{KA + H_m T + H_f T}{(1 + T)}. \quad \text{(Model II)}$$

Model I was investigated separately for males and females and Model II incorporated H_f and H_m. Several other models were also investigated, including:

$$H(T) = \frac{KA + H_m T^P + H_f T^P}{(1 + T)}. \quad \text{(Model III)}$$

In Model III, a power function of the time variable was included.

Goodness-of fit was evaluated based on resulting F-values and the number of parameters used in the model. Parameters were retained in the models with a P-value for inclusion of $P \leq 0.01$. Spearman Rank Correlations were determined to define possible associations between Michigan Alcoholism Screening Test scores, age, heavy alcohol use, frequency of alcohol use, lifetime alcohol use, heart rate and H-values obtained at the week 1 testing date.

3. Results

There were no correlations between initial H-values and heavy alcohol use, lifetime alcohol use, frequency of alcohol use, initial mean IBI, and MAST scores, nor between MAST scores and age, as shown in Table 2.

Visual inspection indicated that with increasing time (T), H values decreased, reaching asymptotic values with longer times of abstinence as shown in Fig. 1. The final model parameters describing the response surface are shown in Table 3. The stratification of H values, PNS and SNS indices by gender and sampling time are shown in Figs. 2 and 3. The strong dependence of initial H values on age at the time of admission (week 1) is shown in Fig. 4.

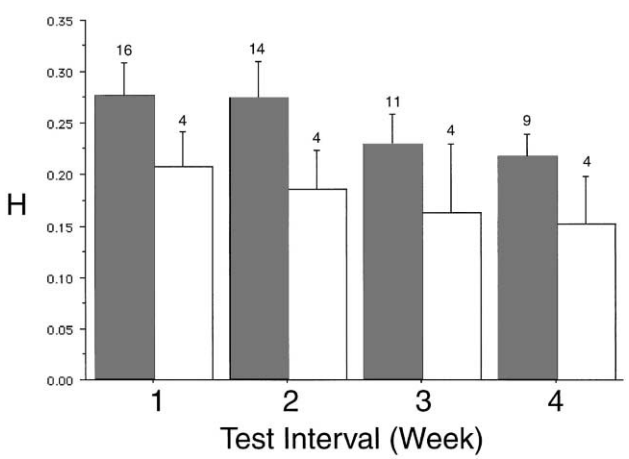

Fig. 2. H values stratified by time-of-testing and gender. The height of the black and white bars represent mean H values from male and female subjects, respectively, along with the associated SEM. The values above the bars represent the n subjects sampled at that time.

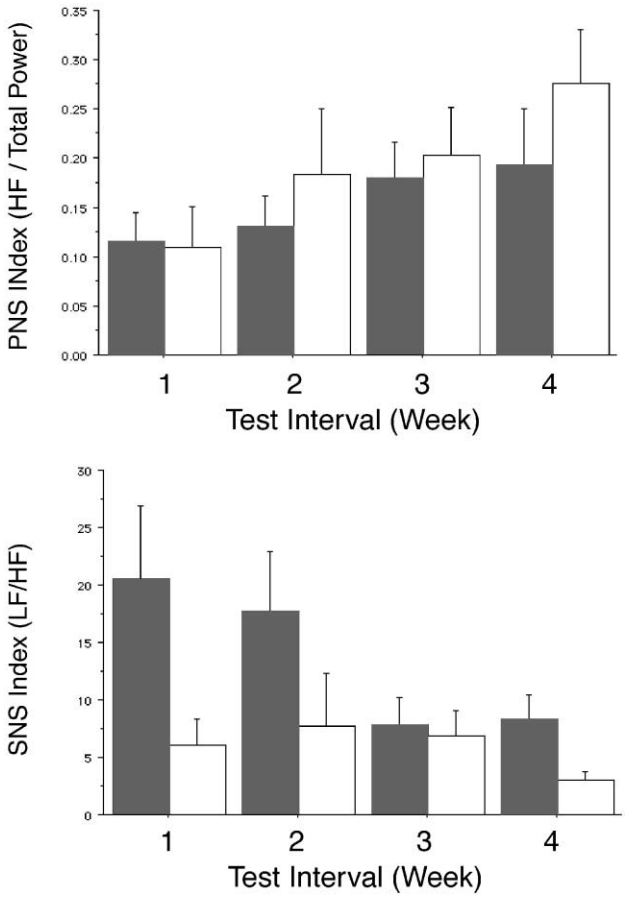

Fig. 3. PNS and SNS indices stratified by time-of-testing and gender. The height of the black and white bars represent mean H values from male and female subjects, respectively, along with the associated SEM. The number of subjects in each group is the same as shown in Fig. 2.

Interbeat intervals at sampling times for weeks 1–4 were (mean $\pm$ S.D., range, in ms), respectively, 783 ± 97, 621–978; 745 ± 87, 607–893; 785 ± 127, 579–1002; 784 ± 96, 687–1002; not significantly different with repeated-measures analysis-of-variance, $P \geq 0.59$.

We compared the final asymptotic H values resulting from the current study with previously determined H values obtained under similar conditions in an outpatient setting, from subjects meeting the criteria for alcohol dependence (age, 40.0 ± 3.8; years, mean $\pm$ SEM) and healthy nonalcoholic comparison subjects (age, 40.3 ± 2.7 years) (DePetrillo et al., 1999a). As shown in Table 4, asymptotic H values in male and female alcoholics were significantly increased at $P \leq 0.05$ compared to age-matched healthy comparison subjects.

4. Discussion

Estimates of parameters that quantify heart rate dynamics are usually obtained from the time-domain or frequency-domain (Stein et al., 1994). The results thus obtained are confounded by the changing statistical properties of heartbeat interbeat interval time series, since physiological signals such as the ECG time series are not stationary (Pilgram and Kaplan, 1999). Time-domain measures such as the mean and standard deviation not only lose all phase and correlation information, but a dispersional measure such as the S.D. is also proportional to the length of the epoch which is analyzed (Kobayashi and Musha, 1982). Also, these analyses proceed under the false assumption that these signals are statistically independent of each other (Eke et al., 2000). Frequency-domain measures also rely on assumptions of stationarity. These criteria are not met with biologically derived physiological data such as the interbeat interval (Weber et al., 1992). These problems are addressed by Hurst analysis, since the resulting parameter provides a more complete and stable characterization of the statistical behavior of the time series. It was previously shown that the estimate of the Hurst parameter was not significantly altered by differences in the mean and standard deviation of time series (DePetrillo et al., 1999b), while estimates of parameters from frequency-domain analyses are not as stable in the presence of differences in time series stationarity. The results of applying both nonlinear and frequency-domain analysis to a set of time series synthesized with the same $1/f$ spectrum but differing stationarity are shown in Table 5. A $1/f$ spectrum was chosen because healthy human IBI time series exhibit this spectral characteristic. (Pilgram and Kaplan, 1999). The estimates of the PNS and SNS indices from the frequency-domain analysis are not as stable as the estimate of the Hurst parameter obtained from the nonlinear analysis, most likely due to the effects of the differing stationarity of the time series. The variance associated with estimates of PNS and SNS indices obtained from human IBI time

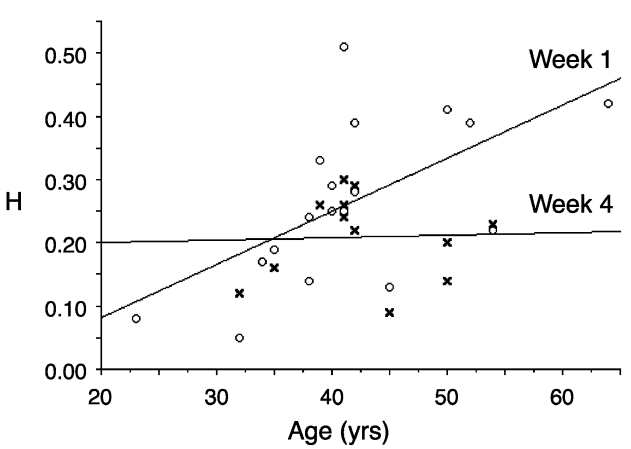

Fig. 4. Linear regression of H values on age obtained at week 1 and week 4. Circles represent values obtained at week 1, and crosses those obtained at week 4. There is a significant correlation between age and H values obtained on admission (week 1) $R = 0.607$, $P \leq 0.008$ and no correlation between values of H and age obtained 28 days after admission (week 4), $R = 0.037$, $P \geq 0.22$.

Table 4
Asymptotic H-values compared to outpatient alcoholic and nonalcoholic Subjects

	Inpatient alcoholic asymptotic $H \pm$ SEM	Outpatient alcoholic $H \pm$ SEM	Outpatient control $H \pm$ SEM
Female	0.16 ± 0.02; $n = 4$[a]	0.09 ± 0.09; $n = 6$	0.05 ± 0.02; $n = 33$
Male	0.24 ± 0.02; $n = 16$[a,b]	0.25 ± 0.04; $n = 7$[a]	0.11 ± 0.02; $n = 15$

[a] Different from outpatient control, $P < 0.05$.
[b] Different from female inpatient alcoholic, $P < 0.05$.

series should be larger in magnitude than that observed for the Hurst parameter, and this is what was observed in the present study. Larger errors are associated with the PNS and SNS estimates in Fig. 3 as compared to Hurst parameter estimates shown in Fig. 2. This suggests that nonlinear analysis may be useful in characterizing the behavior of IBI time series under experimental conditions where there are relatively large differences in means or standard deviations between the different experimental groups, as found in the present study.

When the results of frequency-domain analysis are compared with nonlinear analysis, as shown in Fig. 5, we can see that there is a relationship between the Hurst exponent and the PNS and SNS indices. The H value is inversely proportional to the PNS index and proportional to the SNS index. These results parallel previous reports of an inverse relationship between the PNS index and the Hurst parameter (Yamamoto et al., 1995), suggesting that higher values of H are associated with decreased parasympathetic activity.

A graphical representation of the Hurst parameter is shown by the family of curves depicted in Fig. 6. With increasing times of alcohol abstinence, the H values associated with the interbeat interval time series decrease, which corresponds to an increase in beat-to-beat variability. Graphically, this is perceived as an increase in the roughness of the curves associated with decreased values of H.

A series of asymptotic exponential decay and sigmoid models were explored using the procedures described and illustrated for a subset of the sigmoid family of functions. All exponential decay models tested were rejected as they failed to converge (data not shown). Model III was rejected since with the exception of K, none of the other parameters achieved a significant P-value for retention, as shown in Table 3. When data from male and female subjects were evaluated with Model II, this resulted in an overall F-value that was a significantly better fit than Model I stratified by sex. We therefore reported estimates of K, H_f and H_m resulting from Model II as it provided the best fit to the response surface as all model parameters achieved significance for retention. Sex differences in heart rate variability were found in conjunction with previous results (Ryan et al., 1994). Although the number of

Table 5
Comparison of frequency-domain and nonlinear analyses

Mean of time series ($n = 1000$)	S.D.	log total power	log HF power	log LF power	PNS	SNS	Hurst
600	150.000	4.046	3.330	3.902	0.192	3.734	0.10
	75.000	3.526	2.740	3.405	0.164	4.622	0.13
	37.500	2.830	2.193	2.669	0.230	2.995	0.12
	18.750	2.293	1.532	2.175	0.173	4.388	0.13
	7.500	1.384	0.712	1.212	0.213	3.163	0.13
	3.750	0.888	0.057	0.781	0.148	5.304	0.11
800	200.000	4.408	3.588	4.323	0.152	5.421	0.14
	100.000	3.659	3.041	3.516	0.241	2.987	0.13
	50.000	3.236	2.388	3.158	0.142	5.889	0.13
	25.000	2.519	1.785	2.415	0.185	4.269	0.14
	10.000	1.599	1.021	1.439	0.265	2.613	0.13
	5.000	1.223	0.320	1.155	0.125	6.808	0.13
1200	300.000	4.477	3.858	4.358	0.240	3.167	0.13
	150.000	4.265	3.172	4.228	0.081	11.374	0.13
	75.000	3.573	2.623	3.521	0.112	7.898	0.13
	37.500	2.863	1.956	2.806	0.214	7.068	0.13
	15.000	2.090	1.278	2.017	0.154	5.481	0.12
	7.500	1.518	0.638	1.456	0.132	6.573	0.12

S.D. = standard deviation; PNS = HF/total power; SNS = LF/HF.

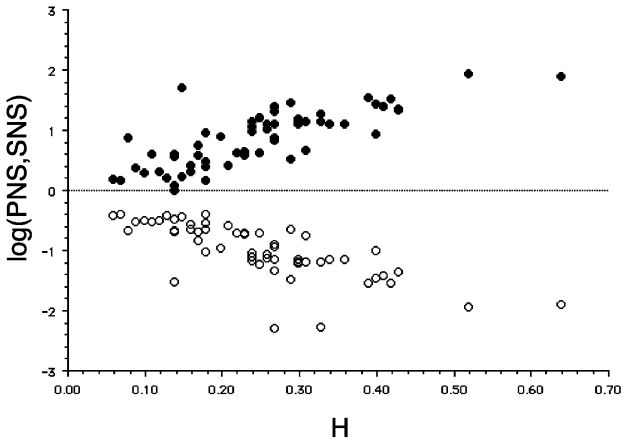

Fig. 5. Relationships between the Hurst exponent and PNS and SNS indices. The filled circles are associated with SNS index, and open circles with PNS index.

females examined in this study was relatively small ($n = 4$), the effect size was large and in general agreement with past work (DePetrillo et al., 1999a).

The sigmoid family of functions have been used to describe dose-responses to a variety of toxicants (Meibohm and Derendorf, 1997). There are no preceding reports relating the time-dependent effects of alcohol abstinence on cardiac signal dynamics. While the effects of abstinence on cardiac left ventricular function have been previously evaluated, the specific relationship between the time interval of abstinence and functional status were not reported (La Vecchia et al., 1996).

The asymptotic H values obtained from the current study were compared to historical control and alcoholic values, as shown in Table 4. In both studies, male alcoholic subjects were found to have similar values of H. The increased variance in H values, especially evident in female outpatient alcoholics in the previous study, may have been due to a wider range of alcohol exposure in a population sampled in an outpatient setting, while only subjects with significant alcohol use histories were admitted to the inpatient unit for treatment.

The age of the subject was found to be the primary determinant of H values at shorter abstinence times and was not sex-dependent. Increased age is associated with decreased heart rate variability (Iyengar et al., 1996). Therefore, our finding that the initial effect of age decreases with time was unexpected. This may be due to the heterogeneous characteristics of the study population, relatively small n, and subsequent Type II error. It could also be interpreted to mean that the effects of alcohol exposure on cardiac rhythm dysregulation predominates over age as an explanatory variable. Given that decreased heart rate variability has been associated with sudden death (Hohnloser et al., 1999), this finding may indicate that older individuals are at higher risk for cardiac arrythmias after chronic excessive alcohol use, which is strongly supported by epidemiological data (Wannamathee and Sharper, 1992; Britton and McKee, 2000).

No significant differences were found in the magnitudes of the interbeat interval across the testing times, suggesting that nonlinear measures such as used in this study are more sensitive indicators of cardiac rhythm dysregulation than measurements performed in the time-domain. Also, the signal magnitude obtained at initial testing was not significantly higher than signal magnitudes obtained at later time points, arguing against the presence of noticeable hyperadrenergic symptoms of alcohol withdrawal at initial testing time.

In humans, parasympatholysis has been shown to increase the H values of the ECG time series (Yamamoto et al., 1995). However, alterations of heart rate variability after parasympatholysis do not occur in the absence of central nervous system input and modulation (Bailey et al., 1996; Setty et al., 1998). In the absence of central modulation, vagal stimulation did not alter measures of heart rate variability (Bailey et al., 1996), even while interbeat interval magnitude increased. Thus, while decreases in heart rate variability resulting from chronic alcohol exposure may be due to sustained decreases in parasympathetic nervous system activity, an alteration in feedback between central and peripheral determinants of heart rate might also explain the results.

Diazepam may have still been present in a small number of subjects at the time of the first testing procedure because of its relatively low clearance. Diazepam may be associated with increased heart rate variability after acute administration (Ikeda et al., 1994). If this effect was

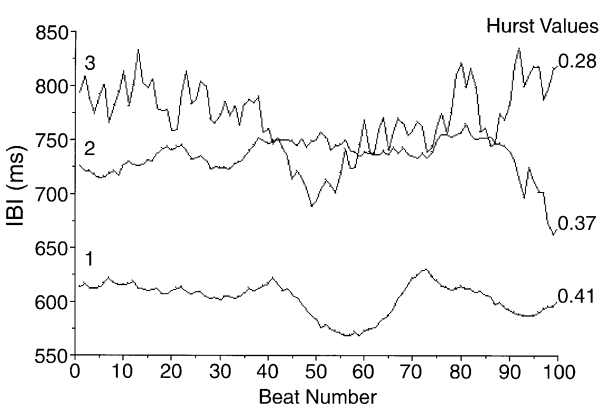

Fig. 6. The interbeat intervals (IBI, ms) and beat number for an epoch of 100 heartbeats is shown for an individual subject sampled three times 7 days apart. On the right of the curves are shown the respective H values associated with the time series, while on the left are shown the time intervals during which sampling occurred. The H value progressively decreases with repeated sampling, corresponding to increased time from last alcohol use. For curves 1–3, mean ± S.D., coefficient of variation are respectively: 603.08 ± 15.06, 0.03; 734.68 ± 18.20, 0.03; 770.43 ± 33.07, 0.04.

present in the current study, it would have biased the results against finding a significant change in heart rate variability measures over time.

In summary, the results of the current study support the hypothesis that cardiac signal dynamics are altered in alcoholics and are characterized by lower heart rate variability as compared to nonalcoholics. This implies that chronic excessive alcohol use may be associated with longer-term alterations in cardiac rhythm than previously suspected, and could indicate irreversible alcohol-related effects on cardiac rhythm regulation. Since a history of alcohol dependence appears to have a large effect in determining heart rate variability even after short-term abstinence, a history of alcohol use or dependence should be included as explanatory variables in population studies examining heart rate variability as an outcome variable.

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