Effect of dietary omega-3 fatty acid deficiency on heart rate variability in hooded rats

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Abstract

Introduction: Recent reports in adult humans suggest that heart rate variability is modulated by the concentration of omega-3 polyunsaturated fatty acids (PUFA) contained in blood cell membranes.
Material and methods: Hurst analysis of ECG data was conducted on 12 male adult hooded (Long-Evans) rats, representing the 3rd generation to be fed diets that were either deficient in, or supplemented with, omega-3 PUFA. ECG data were obtained from surface electrodes and 4000 beats were analyzed for each animal.
Results: Dietary manipulation, despite leading to large changes in tissue omega-3 PUFA levels, did not significantly affect the complexity of heart rate dynamics, with Hurst exponent (*H*) values of 0.15±0.02 and 0.12±0.03, for animals fed omega-3 fatty acid-adequate and -deficient diets, respectively. Mean heart rate was also unaffected by the diets. A power calculation revealed that about one hundred animals per group would have been required to avoid a type II error.
Conclusions: According to this model of dietary PUFA manipulation, omega-3 fatty acids are unlikely to exert a large effect on the autonomic functions that control heart rate variability. Prospective studies into the effect of omega-3 fatty acids on HRV should consider the need for large sample size as estimated by the results contained in this report.

Key words: omega-3 fatty acids, heart rate variability (HRV), Hurst exponent.

Introduction

Moment-to-moment variation in heart rate, which reflects the influence of autonomic tone on cardiac function, serves as a powerful prognostic indicator for survival following myocardical infarction [1, 2]. Some studies [3-7], but not all [8] suggest, in both healthy human adults, and survivors of myocardial infarction (MI), a relationship between omega-3 PUFA content in blood cells and altered heart rate dynamics. The above-mentioned studies by Christensen and colleagues are in agreement that increased omega-3 levels are correlated with an increase in heart rate variability (HRV), as measured using time-domain analyses, though the mechanisms that

modulate these effects are yet to be elucidated. However, these studies did not find increases in HRV following short-term dietary supplementation with omega-3 PUFA.

Heart rate dynamics are usually estimated using parameters obtained from time-domain or frequency-domain analyses [9, 10]. Results obtained with these methods are confounded by the changing statistical properties of heartbeat interval time-series over time, i.e. non-stationary signals. These signals are difficult to interpret with dispersional measures in the time-domain, such as the standard deviation, because the results are not stable with increasing data length. Additionally, these measures do not give any information regarding the internal dynamics of the time-series. Frequency-domain measures rely on assumptions of stationarity that are not met with interbeat interval (IBI) data, especially with longer recording times.

We have used a technique that measures the internal dynamics of an IBI time-series by calculating the Hurst exponent (*H*). The Hurst exponent is a direct measure of the dynamics of a time-series, conceived by Hurst [11] and formalized by Mandelbrot [12]. The value of *H* varies, with $0 \leq H \leq 1$. Visual inspection of a time-series with $H=1.0$ (as shown in Figure 1C), reveals an overall relative smoothness to the graph of IBI versus time. As *H* tends towards 0, trends are more rapidly reversed (Figure 1B, $H=0.05$), where there are large variations between adjacent values, which give it a very irregular look. When $H=0.5$, (Figure 1D), the magnitude of the sequential points of the time-series are independent (of one another) and therefore uncorrelated. The time-series can be considered a random walk. Thus, *H* values approaching 0.5 from either extreme are symptomatic of a breakdown in the long-range correlations of the heart interbeat interval signal. Inasmuch as these long-term correlations are associated with cardiac health [13], Hurst analysis of heart interbeat intervals can provide a measure of cardiac signal complexity in relationship to disease states, and, as in this study, to differing neural fatty acid profiles, subsequent to dietary manipulation. Furthermore, since the measure *H* is not significantly altered by changes in data length, statistical moments, or means of the signal [14], it allows comparisons of cardiac signal complexity measures between different studies.

Cardiac signal complexity is related to the autocorrelation of the interbeat interval time-series. The increased autocorrelation is manifested by increased beat-to-beat variability for the time-series as *H* approaches 0. For these time-series, the parameter *H* corresponds to increased heart rate variability (HRV). Note however that increased autocorrelation is seen as *H* diverges from the value 0.5 (random walk) towards either 1 or 0. Therefore, the degree of autocorrelation is relatively equivalent to HRV measures only for time-series with $0 \leq H \leq 0.5$.

The term HRV will be used as a descriptor of beat-to-beat variability, in accordance with current usage. For interbeat interval time-series, *H* is a measure of both HRV as well as cardiac signal complexity. Therefore, increases or decreases in *H* correspond to decreases or increases in HRV, respectively.

A time-domain measure such as standard deviation, a classic descriptor of variance in data, does not always correlate with HRV. This is because the relationship between each interbeat interval is lost. This point is illustrated in Figure 1. All time-series represented in Figure 1B-1D were generated, as outlined in the methods, to have the same mean and standard deviation as an IBI time-series obtained from one rat, (mean±SD 154.9 ms ±8.3), shown in Figure 1A. The time-series from the animal had an associated *H* value of 0.05±0.02. By visual inspection, the "roughness" of this time-series best matches the synthesized IBI series from Figure 1B, with $H=0.05$. It can also easily be seen that beat-to-beat variability is highest as *H* approaches 0.

The current methodology allows a better representation of the internal dynamics of the system than can be obtained from simple dispersional measures such as mean and standard deviation. Inasmuch as a spectral transform of the IBI data is not required prior to analysis, short lengths of IBI data with differing statistical characteristics can be compared.

We used this technique to determine *H* using IBI time-series data obtained from rats raised on diets that differed in the amount of omega-3 fatty acids supplied in the diet. Since decreases in heart rate variability (HRV) are associated with higher values of *H* [14], we surmised that a higher *H* value would characterize ECG data from omega-3 deficient rats when compared with those raised on an omega-3 adequate diet. We are not aware of any other study to assess the effects of severe omega-3 PUFA deficiency on HRV using Hurst analysis.

Material and methods

Animals and diets

All procedures involving animals were conducted in accordance with local Animal Care guidelines and were approved by the NIAAA Animal Ethics Committee.

Animals in this experiment were raised on one of two semi-purified diets (Table I). Dietary fats were supplied by the supplementary oils added to the diets, thus creating one diet deficient in omega-3 fatty acids (n-3 DEF), and the other omega-3 adequate with the addition of pre-formed DHA (n-3 ADQ). The assayed fatty acid compositions of both experimental diets are given in Table II. Other details regarding the composition of the salt and vitamin mixes have been described previously [15].

Animals were successively raised for three generations (F3), as previously reported by this and

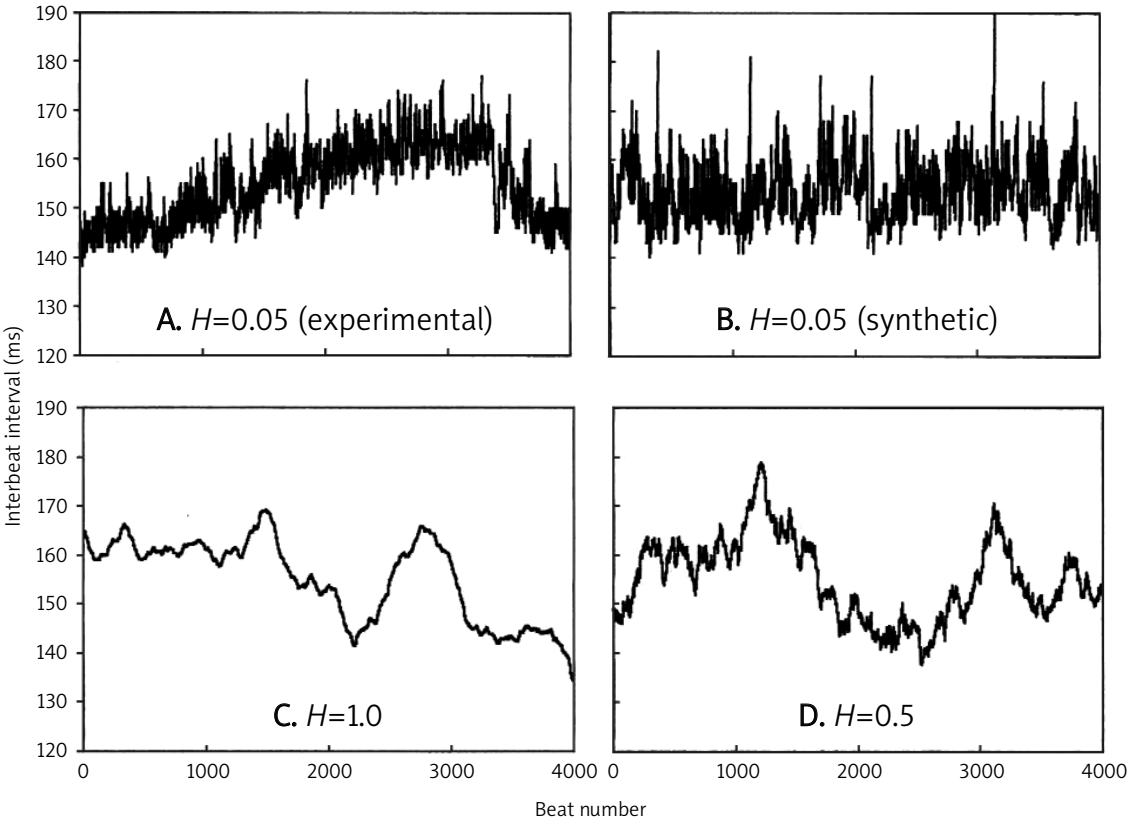

Figure 1. Illustration of the Hurst coefficient as it relates to cardiac IBI time-series. The ordinate-axis represents the IBI in milliseconds (ms) and beat number is represented by the abscissa. The time-series B-D were synthesized according to the methods to correspond with the *H*-value shown in the bottom right corner of each graph. The time-series represented in A is from one rat used in the study, and the *H*-value is derived using Hurst analysis

other laboratories [16-19]. Twelve (12) F3 male, hooded rats (Long-Evans) were used for the study (though we failed to obtain data from one of the rats). Animals were fed once per day with dietary pellets and water *ad libitum*. The ambient light was cycled in the animal room (12/12 light/dark cycle), with temperature maintained at 70°F. Animals were 33 weeks old, and matched for bodyweight at the time of testing (mean ±SD; n-3 DEF: 878±44 g; n-3 ADQ: 881±40 g).

Experimental procedure

ECG IBI data were collected as follows. Individual rats were placed in an anesthesia chamber containing isoflurane (Baxter, Deerfield, IL) for approximately 30 seconds. Upon sedation, animals were transferred to a downdraft table, where they were maintained under anesthesia via a nose-cone. The electrode positions corresponding to the maximal *QRS* potential was determined using subcutaneous needle electrodes, attached to a CD-200 oscilloscope monitor. Typically, this was 1 cm rostral to the sternal notch, with a lateral separation of approximately 3 cm either side of the midline. The chest wall was shaven, and surface ECG electrodes fixed with conductive gel and fast-setting glue. The contact was further protected by tape and a custom-made jacket and harness system that allowed unrestricted movement upon waking. Animals were allowed to awaken from anesthesia following the setup procedure, which took 12-15 minutes.

Electrodes were wired to a Polar belt (Polar Electro, Woodbury, NY), in communication with a Mini-logger Series 2000 (Mini-mitter, Sun River, OR, USA), which was used to store the IBI data. The logger configuration was adjusted in consultation with the manufacturer to allow reliable capture of IBIs corresponding to heart rates in the order of 400 beats per minute. The sampling rate for the device is 500 Hz and results in a timing accuracy of <1 ms in the measurement of the IBIs [20]. IBIs were measured from the time of electrode contact until 2 hours after awakening, such that approximately 45,000 IBIs were recorded for each animal. Following the recording period, animals were briefly anesthetized again to enable removal of the electrodes and harness. Soon after completion of the HRV study, animals were

Table I. Compostion of semi-synthetic diets

Component	(g/kg)	
Casein, vitamin-free	200	
Carbohydrate	600	
Cornstarch	150	
Sucrose	100	
Dextrose	199	
Maltose-Dextrin	150	
Cellulose	50	
Salt mix	35	
Vitamin mix	10	
L-Cystine	3	
Choline bitartate	2.5	
TBHQ	0.02	
Fat	100	
Fat sources (%)	**n-3 DEF**	**n-3 ADQ**
Coconut oil	81	74.49
Safflower oil	19	17.7
Flaxseed oil	–	4.81
DHASCO	–	3

Table II. Fatty acid composition of diets

Fatty acid	n-3 DEF diet	n-3 ADQ diet
8:0	0.8	2.1
10:0	3.8	3.9
12:0	39.7	35.3
14:0	16.7	15.5
16:0	9.8	9.5
18:0	9.7	9.0
20:0	0.2	0.2
22:0	0.1	0.1
24:0	0.1	0.1
Total saturated	80.8	75.7
16:1n-7	0.03	0.03
18:1n-9	3.5	4.4
18:1n-7	0.3	0.3
20:1	0.1	0.1
22:1	0.01	0.02
Total monounsaturated	3.9	4.8
18:2n-6	15.1	15.7
20:2n-6	0.05	0.06
Total n-6	15.1	15.8
18:3n-3	0.04	2.5
22:6n-3	–	1.3
Total n-3	0.04	3.8
18:2n-6/18:3n-3	345	6
n-6/n-3	346	4
Total PUFA	15	20

Values expressed as percentage of total fatty acid weight

decapitated. Brain lipid composition was determined using a lipid extraction method modified after Schwertner [21], and fatty acid analysis as described by Salem et al. [22]. As HRV is primarily a measure of central function, cardiac tissue was not obtained.

Data analysis

Cardiac IBI data, in milliseconds, were retrieved from the Mini-Logger using Version 3.5 of the Mini-Logger software on an IBM Pentium II personal computer running Windows NT. The IBI data were filtered using linear interpolation if any single IBI was more than twice the magnitude of the previous IBI. In most animals, the amount of filtering required was less than 5% (range 0-10%; mean±SEM, 3.8±1.4%). There were no differences in filtering between the two experimental groups. Data was analyzed as previously reported [14, 23] using software incorporating an algorithm which extracts the fractal dimension *D* of the time-series, and derives the Hurst value as $H=2-D$. The software application used for these analyses, running on Windows NT, 95 or 98 (Microsoft, USA), is available and can be obtained through a procedure outlined at ftp://helix.nih.gov/pbdp.

The value of the embedding constant used for the analysis was estimated by increasing the embedding dimension in increments of 1 until *D* reached a stable value. Empirical testing showed that a dimension of 12 resulted in a stable measure of *D* for all time-series tested.

H was determined for one continuous 4000 beat sequence (approximately 10 minutes), which commenced 90 minutes after the animal awoke. We chose this period to enable maximal recovery from anesthesia, while still maintaining a good surface electrode contact. Analysis of variance (ANOVA) and the Mann-Whitney sum of ranks were calculated (Sigmastat, SPSS) to determine whether there were differences in the values of *H* or IBI magnitude between animals raised on the n-3 ADQ versus n-3 DEF diets.

Results

The r^2-value for the linear regressions used for the calculation of *H* values were all 1.00, suggesting that a strong scale-dependent power law relationship [24] applies to the hooded rat IBI time-series. The

relationship of the IBI time-series and the calculated *H* parameter is shown for one animal in Figure 2.

Heart rate was observed to increase (i.e. a decrease in IBI) as the animal recovered from anesthesia, as shown in Figure 2. The observed effects of isoflurane on heart rate variability are not discussed in this report, and will be presented elsewhere.

As shown in Table III, despite the profound influence of the diets on the level of DHA in the brain, the value for H was not affected. However, the power of the ANOVA performed was far lower (0.05) than that considered acceptable to avoid a Type II error (i.e. 0.8). The sample size required to adequately detect a significant difference was calculated assuming a Normal distribution, equal variances and a two-sided alternate hypothesis using Equation 1,

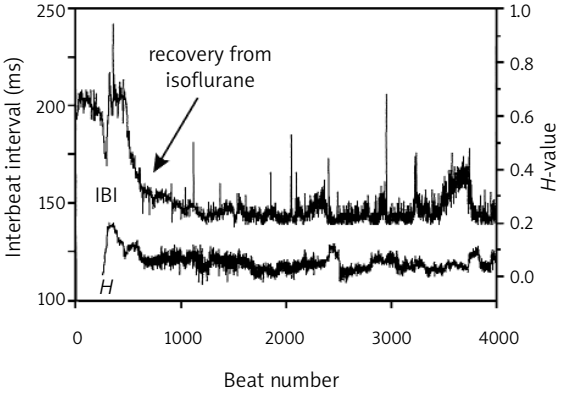

Figure 2. Representative rat IBI tracing (upper) and corresponding *H*-value (lower). Note the increase in heart rate (decrease in IBI) following removal of isoflurane anesthesia

$$n = \frac{(\sigma^2_{ADQ} + \sigma^2_{DEF}) \times (Z_{1-\alpha/2} + Z_{1-\beta})}{\Delta^2}$$

in which *n* is the sample size required in each group to detect a difference in mean *H*-value of Δ (with α=0.05 and power $(1-\beta)$=0.8). σ_{ADQ} and σ_{DEF} are the standard deviations for measures of *H* in the two diet groups. It was revealed that approximately 200 animals (100 from each dietary group) would have been required for this study, in which Δ represented a difference of approximately 20%.

Discussion

Changes in heart rate are primarily determined by autonomic innervation, whereby parasympathetic activation slows heart rate and sympathetic tone increases it [25]. Hence, the moment-to-moment variability of heart rate is an index of autonomic nervous system function. One likely mediator of HRV control is the type-3 serotonin receptor (5-HT_3), since pharmacological manipulations of this receptor's activity profoundly alter HRV [26]. Pronounced changes in HRV have been found in various disease states, most notably, alcoholism [23]. Moreover, assessment of HRV provides a means of stratifying risk for sudden cardiac death, or death following acute MI [27, 28]. Given the importance of HRV as both an index of neural integrity, and as a prognostic indicator in clinical medicine, it is not surprising that the study of HRV generators and the factors which may potentially modulate them has attracted considerable research interest [1, 2].

The present study assessed the effects of extremes of tissue omega-3 PUFA on HRV, with the neural omega-3 PUFA levels of those fed the omega-3 deficient diet less than one-third that of those fed the omega-3 adequate diet. Despite these large differences, we failed to find a significant effect of dietary omega-3 fatty acids on HRV (Table III). Furthermore, we did not find an effect on heart rate, though others have reported a decrease in HR with omega-3 supplementation [8, 29, 30]. Moreover, the study would have required a large number of animals to avoid a type II error.

Our results differ from some reports on humans, following supplementation with dietary omega-3 fatty acids. The discrepancies may be explained by several differences between this study and the numerous human clinical trials, though aside from

Table III. Effect of diet on whole brain DHA, *H*, inter-beat interval and heart rate

	Diet Group	
	n-3 ADQ (n=5)	n-3 DEF (n=6)
Brain DHA (% total lipid)	10.8±0.3*	3.4±0.5
H	0.15±0.04	0.12±0.07
Inter-beat interval (ms)	159.3±9.3	161.0±13.3
Heart rate (beats/min)	377.6±21.6	374.6±28.2

Values expressed as mean ±SD
**Greater than n-3 DEF (p<0.05)*

one clinical trial on survivors of myocardial infarctions, positive associations between omega-3 fatty acids and higher HRV were only found after *post hoc* analyses, which dichotomized the treatment groups by plasma omega-3 concentrations [3-6, 31, 32]. The conclusions drawn, though informative, are not definitive for several reasons. Firstly it is well known that blood PUFA profile does not necessarily reflect neural accretion levels [33, 34], unless the level of consumption has been maintained for some months. Rather, blood cell PUFA profile is a reflection of the current (or recent past) level of dietary fatty acid consumption. If HRV was correlated with blood PUFA profile, one would also expect a significant change with omega-3 supplementation in an interventional prospective study. Hence, the conclusions made following dichotomization are inconsistent with the failure to find a treatment effect. Secondly, the reported increases in the standard deviation of *RR* interval (SDNN), as an indicator of increased HRV following dietary omega-3 supplementation, did not consider a parallel increase in mean *RR* interval. Since the SDNN is intrinsically related to the mean *RR* interval, increases in the mean will necessarily increase the SDNN, thereby confounding the interpretation of the results. Additionally, our failure on finding a treatment effect may be due to species differences in comparing rodents and humans, and that our study did not directly use dietary eicosapentaenoic acid, whereas the human trials did. Furthermore, the experimental models differed in that these rats were omega-3 deficient throughout neurodevelopment while the human subjects were supplemented as adults.

Though ketamine is typically used in small animal studies, it has been shown to exert marked effects on *N*-methyl-*D*-aspartate (NMDA) receptors, which, in turn, have been implicated in reflex control of cardiac rhythm [26, 35, 36]. In contrast, isoflurane is believed to act on γ-amino-butyric acid (GABA) receptors, though its mechanism of action is unclear. Furthermore, since isoflurane has very fast transport clearance [37] and is not significantly metabolized [38], we believe that our measures of HRV were not significantly affected by anesthesia. Indeed, though several reports have demonstrated generalized power reductions for frequency-domain measures of heart rate [39, 40], these do not appear to persist following recovery [41].

Conclusions

We conclude that, according to this model of dietary PUFA manipulation, omega-3 fatty acids are unlikely to exert a large effect on the autonomic functions that control heart rate variability. Prospective studies into the effect of omega-3 fatty acids on HRV should consider the need for large sample size as estimated by the results contained in this report.

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