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HEART RATE VARIABILITY ANALYSIS: HIGUCHI AND KATZ'S FRACTAL DIMENSIONS IN SUBJECTS WITH TYPE 1 DIABETES MELLITUS

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Abstract

Background and aims: *Statistical markers are valuable when assessing physiological status over periods of time and in certain disease states. We assess if type 1 diabetes mellitus promote modification in the autonomic nervous system using the main two types of algorithms to estimate a Fractal Dimension: Higuchi and Katz.* ***Material and methods:*** *46 adults were divided into two equal groups. The autonomic evaluation consisted of recording heart rate variability (HRV) for 30 minutes in supine position in absence of any other stimuli. Fractal dimensions ought then able to determine which series of interbeat intervals are derived from diabetics' or not. We then equated results to observe which assessment gave the greatest significance by One-way analysis of variance (ANOVA1), Kruskal-Wallis technique and Cohen's d effect sizes.* ***Results:*** *Katz's fractal dimension is the most robust algorithm when assisted by a cubic spline interpolation (6 Hz) to increase the number of samples in the dataset. This was categorical after two tests for normality; then, ANOVA1, Kruskal-Wallis and Cohen's d effect sizes ($p \approx 0.01$ and Cohen's $d=0.814143$ –medium effect size).* ***Conclusion:*** *Diabetes significantly reduced the chaotic response as measured by Katz's fractal dimension. Katz's fractal dimension is a viable statistical marker for subjects with type 1 diabetes mellitus.*

key words: *diabetes, dynamical diseases, katz, higuchi, fractal dimension, cubic spline interpolation*

Background and aims

Statistical markers are advantageous when reviewing healthy physiological status or different pathological states which can develop over extended periods of time. They can be enforced to assess whether certain aspects of lifestyle are beneficial or problematic. Many of the most widely used markers in clinical medicine are based on assessing the signals generated by the heart rhythm. These cardiac interbeat intervals (RR intervals) have been revealed to fluctuate in a complex and sometimes chaotic manner [1]. Heart rate variability (HRV) is useful for assessment of many conditions or different types of diseases

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[2-4] which include type 1 diabetes mellitus (T1DM) [5-7], immune responses such as inflammation [8-10], psychiatric states such as schizophrenia [11] and bi-polar disorder [12] and cardiovascular diseases [13,14]. Usually, a higher HRV indicates a favourable general health and wellbeing [15] with less risk of morbidity or mortality and low HRV can provide an indicator of the risk of "dynamical diseases" [16].

HRV is a simple, reliable, non-invasive and cost effective method of monitoring the autonomic nervous system (ANS). Other procedures for assessing ANS comprise photoplethysmography [17], phonocardiography [18] and vibrocardiography [19]. Some methods are unresponsive as with sympathetic skin response [20] or too complicated and expensive as with quantiative pupillography [21]. All the other alternatives have potential hazards, so HRV became widely used.

Fractal systems exhibit a characteristic termed self-similarity. A self-similar object upon close examination reveals it is composed of smaller versions of itself. Fractal analysis has a statistical advantage over other techniques enforced on short time-series, such as chaotic globals [5,22], in that the phase information is preserved. Phase information is lost in methods involving power spectral analysis [6].

There are many algorithms which can be applied to estimate a Fractal Dimension. There are those by Higuchi [23], Katz [24], Petrosian [25] and Castiglioni [26]. We assess if T1DM promote modification in the autonomic nervous system by assessing their HRV using the main two types of algorithms to estimate a Fractal Dimension; those by Higuchi [23,27] and Katz [24]. These are regarded as the two most statistically robust methods.

Material and Methods

Patient Selection and Assessments were consistent with previous studies by Souza *et al.* [5] and Garner *et al.* [6].

Higuchi Fractal Dimension (HFD)

In 1988 Higuchi derived his procedure to measure the fractal dimension of discrete time sequences. It is regarded as the most robust of all the fractal dimension techniques and can be enforced on relatively short sections of data. It is imposed directly to the RR intervals with no power spectrum step as would be the case with the chaotic globals [5,6]. Khoa *et al* [27] presented the algorithm and we adapt it below for RR intervals.

It is based on a measure of length, L*(k),* of the curve that represents the considered time-series while using a segment of k samples as a unit, if L*(k)* scales in the following manner:

$$L(k) \sim k^{-Df}$$

The curve is alleged to display a fractal dimension D_f. A simple curve has dimension equal to 1 and a plane has dimension equal to 2. The value of D_f is always between 1 (a simple curve) and 2 (a curve which almost fills out the whole plane). D_f quantifies the complexity of the curve and so of the time-series this curve represents on a graph.

From a given time series, *RR(1), RR(2), ... , RR(N),* the algorithm constructs k new time series:

$$RR_{km} = \left\{ RR(m), RR(m+k), RR(m+2k), ..., RR\left(m + int\left(\frac{(N-m)}{k} \right) \cdot k \right) \right\} \; for \;\; m = 1, 2, ...k,$$

where m is initial time value, k indicates the discrete time interval between points, hence the delay, k_{max} is maximum interval time, int(a) is integer part of a real number a.

For each of the time-series RR_{km} constructed, the average length $L_m(k)$ is then computed as:

$$L_m(k) = \frac{1}{k}\left[\left(\sum_{i=1}^{int((N-m)/k)} \left|RR(m+i\cdot k) - RR(m+(i-1)\cdot k)\right|\right)\right] \times \frac{N-1}{int\left(\frac{(N-m)}{k}\right)\cdot k}$$

N is total number of RR intervals. Subsequently, the length of the curve for time interval k is expressed as the sum value over k sets of $L_m(k)$ as illustrated by the following equation.

$$L(k) = \frac{1}{k}\sum_{m=1}^{k} L_m(k)$$

Lastly, the slope of the curve $\ln(L(k)) / \ln(1/k)$ is estimated using least squares linear best fit and the resulting slope is the HFD. To select a suitable value for k_{max}, HFD values are plotted against a range of k_{max}. The point at which the fractal dimension plateaus is considered a saturation point. That appropriate k_{max} value should be selected.

Katz's Fractal Dimension

Regarding the Katz's algorithm [24] this fractal dimension is once more calculated directly from the time-series. This algorithm has the advantage over that of Higuchi's in that a k_{max} parameter is superfluous. Yet, it has the difficulty that it requires a longer time-series to achieve significant results. It is important to recall that an accurate value for any type of fractal dimension should be between 1 and 2, as stated in the preceding section (see results later).

$$Katz = \frac{Log10(L/a)}{Log10(d/a)}$$

L is the total length of the time-series and d is the *Euclidean* distance between the first point in the series and the point that provides the furthest distance with respect to this first point. If we set a to be the mean distance between successive points and, n as the number of steps in the curve, then $n = L/a$.

$$Katz\_FD = \frac{Log10(n)}{Log10(d/L) + Log10(n)}$$

Statistical Analysis

Parametric statistics accept that the datasets are normally distributed, hence the use of the mean as a measure of central tendancy. If we cannot normalize the data we should not compare means. To verify normality we imposed the Anderson-Darling [28] and Ryan-Joiner [29] tests. The results were inconclusive so we are unable to assert that the observations follow either a normal or non-normal distribution. So, we applied both parametric and non-parametric tests of significance. These are the one-way analysis of variance (ANOVA1) [30] and the Kruskal-Wallis [31] tests of significance, respectively. To quantify the magnitude of difference between protocols for significant differences, the effect size was calculated via Cohen's d [32]. Large effect size was considered for values greater than or equal to 0.9, medium for values between 0.9 and 0.5 and small for values amid 0.5 and 0.25.

Results

The descriptive statistics of HFD between control and the diabetics (n=23 both), are presented in Table 1. Figure 1 illustrates the similar data as a box-and-whiskers plot. When we assessed the HFD there were no significant results at any levels of k_{max}. We set the level of significance at $p<0.05$ (or <5%) and this was not accomplished at any level of k_{max}. No saturation point was accordingly achieved. Throughout the HFD analysis exactly 1000 RR intervals from the two groups were applied.

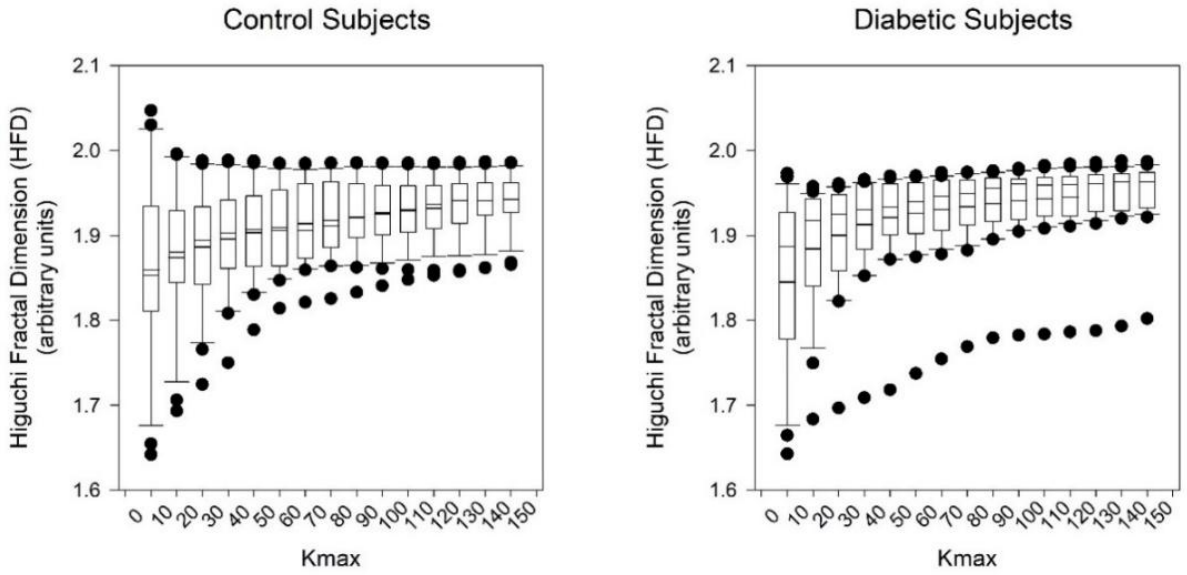

Figure 1. *Box-and-whiskers plot for HFD of exactly 1000 RR intervals of the control subjects (left; n=23) and the diabetic subjects (right; n=23), calculated multiple times from 10 to 150 in equidistant units for different levels of k_{max}. Where the line in the central of the box is the median (not the mean), the whiskers of the outer points are the 10^{th} and 90^{th} percentiles, with the outer edge of the boxes representing the 25^{th} and 75^{th} percentiles. The difference between the outer box edges is the inter-quartile range. The outermost points are the maximum and minimum. The next to outmost points are the 5^{th} and 95^{th} percentiles.*

Table 1. HFD statistics through k_{max} between 10 and 150 at intervals of 10 in the control and diabetic subjects. The statistics include mean and standard deviation HFD for controls and diabetics and their level of significance tested by one-way analysis of variance (ANOVA1), Kruskal-Wallis technique and Cohen's *d* effect sizes. With Cohen's *d* effect sizes, a positive sign implicates a change in mean value in the contradictory direction to the others -- an decrease rather than an increase.

HFD Parameter (k_{max})	Mean HFD Control	±SD HFD Control	Mean HFD Diabetics	±SD HFD Diabetics	ANOVA1 (p-value)	K-Wallis (p-value)	Effect Size Cohen's *d*
10	1.859504	0.108604	1.845075	0.097970	0.638463	0.834677	+0.14265
20	1.874092	0.084811	1.884397	0.074033	0.662824	0.621090	-0.13236
30	1.886559	0.069791	1.900057	0.063663	0.496769	0.435446	-0.20662
40	1.895530	0.059855	1.912839	0.057862	0.324154	0.206507	-0.30065
50	1.903205	0.052310	1.921009	0.054647	0.265130	0.132353	-0.34032
60	1.909394	0.047795	1.925970	0.051197	0.262510	0.144029	-0.34222
70	1.913826	0.045006	1.930586	0.048268	0.229739	0.097182	-0.36722
80	1.917715	0.043227	1.933628	0.045738	0.231735	0.126796	-0.36563
90	1.921586	0.041367	1.937505	0.043443	0.209806	0.144029	-0.38374
100	1.925517	0.039373	1.940905	0.042183	0.207635	0.084603	-0.38560
110	1.928995	0.037496	1.943195	0.042109	0.233561	0.080715	-0.36418
120	1.932180	0.036202	1.945032	0.041724	0.270590	0.101692	-0.33641
130	1.935733	0.034948	1.946806	0.041182	0.330886	0.121423	-0.29645
140	1.938628	0.033736	1.949089	0.039940	0.342487	0.116230	-0.28934
150	1.940530	0.032375	1.951203	0.038177	0.312117	0.101692	-0.30831

Descriptive statistics for the Katz's Fractal Dimension are presented in Table 2.

The number of RR intervals in the dataset was 1000. When the number of RR intervals was 1000 and the metric calculated a fractal dimesion of greater than 2 was achieved which is undoubtedly erroneous. Unlike HFD the Katz's algorithm requires longer time-series. So, we then enforced a cubic spline interpolation [33] at levels 1 Hz to 15 Hz. Then the number of

samples in the datasets enlarged from 1000 to 15000 increasing by 1000 per 1 Hz increase. Again, the statistical tests applied were ANOVA1, Kruskal-Wallis test and Cohen's *d* effect sizes.

Table 2. The mean and standard deviations for the Katz's fractal dimension. There were equal groups of subjects for controls and diabetics (both n=23) and the number of RR intervals in the dataset was 1000. We then enforced a cubic spline interpolation at levels 1Hz to 15 Hz. Then the number of samples in the datasets enlarged from 1000 to 15000.

Cubic Spline Interpolation (Hz)	Mean Katz Control	±SD Katz Control	Mean Katz Diabetics	±SD Katz Diabetics	ANOVA1 (p-value)	K-Wallis (p-value)	Effect Size Cohen's *d*
1	2.254557	0.280286	2.006855	0.380927	0.015753	0.010485	0.757352
2	1.730896	0.152157	1.585150	0.215442	0.011138	0.010485	0.799032
3	1.543622	0.114927	1.431433	0.164505	0.010289	0.011167	0.808403
4	1.441388	0.096276	1.346815	0.138042	0.009932	0.011887	0.812553
5	1.374934	0.084749	1.291723	0.121089	0.009803	0.011887	0.814086
6	1.327409	0.076738	1.252369	0.108971	0.009798	0.011887	0.814143
7	1.291298	0.070729	1.222551	0.099687	0.009871	0.011887	0.813282
8	1.262685	0.065988	1.199021	0.092240	0.010004	0.011167	0.811709
9	1.239321	0.062106	1.179890	0.086065	0.010176	0.011167	0.809703
10	1.219792	0.058833	1.163981	0.080816	0.010383	0.010485	0.807336
11	1.203171	0.056011	1.150512	0.076269	0.010618	0.010485	0.804694
12	1.188815	0.053536	1.138943	0.072270	0.010880	0.010485	0.801814
13	1.176265	0.051333	1.128888	0.068712	0.011166	0.009841	0.798744
14	1.165185	0.049349	1.120061	0.065513	0.011471	0.009841	0.795537
15	1.155318	0.047544	1.112246	0.062614	0.011796	0.009841	0.792217

The best metric and the only one to give significant results on all three statistical tests of significance was Katz's algorithm. There was a high level of significance for the Katz's algorithm ($p \approx 0.01$, ≈1%; both ANOVA1 and Kruskal-Wallis tests) and a medium effect size (0.814143) for a cubic spline interpolation of 6 Hz.

Discussions

Formerly when manipulating short-time series for the assessment of chaotic response in diabetic subjects we have computed the chaotic global techniques [22,34] to discriminate between control subjects and those with type I diabetes mellitus [5,6]. Generally, these chaotic global techniques are sufficient but due to the power spectral step the phase information is lost. This then was the motivation to apply the same data to fractal dimension techniques. Here the phase information is preserved. Fractal dimensions are less computer processor expensive and so quicker to calculate.

Firstly, the HFD technique. In this case HFD was revealed to be inferior when the ANOVA1, Kruskal-Wallis and Cohen's *d* tests were applied and thus gave insignificant values for all levels of k_{max}.

Yet, there was a significant decrease in chaotic response measured by Katz's fractal dimension of HRV in diabetic subjects. Consequently, diabetes could lead to risk of dynamical diseases and those mentioned in the introduction. The extent of this is revealed by Katz's fractal dimension on short time-series. This is a useful statistical marker for the assessments of patients with diabetes, for example under pharmacological treatments or numerous other factors which potentially cause changes in the HRV.

The Katz's algorithm can be enforced as a statistical marker for the detection of diabetic subjects from the controls. This can also be

useful as a risk assessment from dynamical diseases and other physiological conditions such as strenuous exercise [35], an immune response [8-10], obesity [36,37] malnutrition [38], experiencing traffic noise [39], or just getting older [34,40], all of which can affect the HRV. It is therefore a guide to the probability of mortality or morbidity.

Conclusions

Higuchi and Katz's fractal dimensions were assessed. It was revealed that only Katz's fractal dimension discriminates between the two groups. This was achieved with recorded data of 1000 RR intervals. Yet, 6000 samples computed via a cubic spline interpolation of 6Hz was required to enable maximal discrimination between diabetics and normals.

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