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RISK ASSESSMENT OF DIABETES MELLITUS BY CHAOTIC GLOBALS TO HEART RATE VARIABILITY VIA SIX POWER SPECTRA

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Abstract

Background: *The priniciple objective here is to analyze cardiovascular dynamics in diabetic subjects by actions related to heart rate variability (HRV). The correlation of chaotic globals is vital to evaluate the probability of dynamical diseases.* ***Methods:*** *Forty-six adults were split equally. The autonomic evaluation consisted of recording HRV for 30 minutes in supine position without any additional stimuli. "Chaotic globals" are then able to statistically determine which series of interbeat intervals are diabetic and which are not. Two of these chaotic globals, spectral Entropy and spectral Detrended fluctuation analysis were derived from six alternative power spectra: Welch, Multi-Taper Method, Covariance, Burg, Yule-Walker and the Periodogram. We then compared results to observe which power spectra provided the greatest significance by three statistical tests: One-way analysis of variance (ANOVA1); Kruskal-Wallis technique and the multivariate technique, principal component analysis (PCA).* ***Results:*** *The Chaotic Forward Parameter One (CFP1) applying all three parameters is proven the most robust algorithm with Welch and MTM spectra enforced. This was proven following two tests for normality where ANOVA1 (p=0.09) and Kruskal-Wallis (p=0.03). Multivariate analysis revealed that two principal components represented 99.8% of total variance, a steep scree plot, with CFP1 the most influential parameter.* ***Conclusion:*** *Diabetes reduced the chaotic response.*

key words: *diabetes; power spectra; principal component analysis; complexity; chaos*

Background and Aims

The beat of cardiac interbeat intervals has been revealed to oscillate in a complex and possibly chaotic manner [1]. It is the aim to optimally assess the pathological risk that levels of diabetes mellitus pose to the individual by analyzing the heart rate variability (HRV). To accomplish this we applied the Shannon Entropy [2] and Detrended fluctuation analysis (DFA) [3] algorithms to six different power spectra to determine which exhibited the most parametric sensitivity. Originally, Garner and Ling [4] undertook this to compute the spectral Entropy [5] and spectral Detrended fluctuation analysis (sDFA) [4]. Yet, power spectra that we applied

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here to derive these two parameters are: Welch [6], Multi-Taper Method (MTM) [7,8], Covariance [9], Burg [9], Yule-Walker [10] and the Periodogram [11,12].

The advantage for producing the correlation with HRV is that it can provide a benchmark of the risk of the so-called "dynamical diseases [13]" in diabetic subjects. A potential reduction would be consistent with changes in the autonomic nervous system (ANS) and a dysfunctional vagus. The vagus has a vital role in regulating the rhythm of physiological systems. Sympathetic and parasympathetic nervous systems interactions have been documented as influencing HRV.

HRV is a basic tool widely used to monitor the ANS. Alternative techniques include Photoplethysmography [14], Phonocardiography [15] and Vibrocardiography [16]. Some are unresponsive as with Sympathetic Skin Response [17] or too intricate and costly as with Quantiative Pupillography [18].

'Chaotic global' techniques are more responsive to erraticism in dynamical systems than those based on time-domain, geometric methods, frequency domain and/or nonlinear measurements [19]. Chaotic behaviour in biological systems usually indicates normal physiological status; while a reduction of chaotic tendancies could be a pathophysiological marker [20].

By implementing six alternative power spectra we aim to accomplish a result of greater significance by parametric and non-parametric statistics when equating normals with diabetics. It would then be conceivable to reach a diagnosis and provide the necessary treatment earlier.

Material and Methods

Patient Selection and Assessment was identical to the study by Souza *et al*. [21]. In brief, the study consisted of forty-six adults split equally. A cohort with diabetes mellitus (type 1); male (44%) and a control group of healthy subjects; male (65%).

The subjects were selected for the absence of cardiac and respiratory diseases, non-administration of medication(s) and were non-smokers and non-alcoholics. Those subjects who satisfied the inclusion criteria progressed to an explanation of the objectives and procedures of the study and signed a confidential informed consent form. All of the procedures in this study were agreed by the Research Ethics Committee of the institution (Protocol No 47/2011). The experimental protocol consisted of the identification and autonomic evaluation. Throughout the identification, details were logged of the subjects past medical history to determine whether they satisfied the inclusion criteria and to characterize the population. The physical evaluation was undertaken by quantification of HRV. Appraisals were conducted in a noiseless laboratory with the temperature at about 23°C and humidity around 54%. All assessments were performed between 13:00hr and 17:00hr to circumvent circadian cycle influences.

Data with regards to age, gender, signs and symptoms resulting from diabetes, the use of medications, smoking and alcoholic intake and the extent of physical activity judged by international physical activity questionnaires [22], were collected from the subjects.

The HRV evaluations were undertaken to verify the autonomic modulation. The subjects were instructed to avoid alcoholic and/or ANS stimulants for 24 hours prior to data recording. Throughout the autonomic evaluation, the subjects were told to remain alert, silent, with spontaneous breathing at rest, in the supine position for 30 minutes on a sofa. After receiving an explanation of the data collection procedures, an electrode was located on the

subjects' torso, and the heart rate receiver (Polar Electro, model S810i, Finland) was placed around the patients' wrist. The equipment had been validated for collecting HRV data for analysis [23]. To analyze HRV indexes, precisely 1000 intervals of successive cardiac beats were recorded. They were chosen after digital filtering and perfected by manual filtering to eliminate artifact and ectopic beats. Only the series exceeding 95% of sinus beats were included.

In the past, we have applied the Welch and MTM power spectra. It was assumed that since the MTM is an adaptive and nonlinear technique with less spectral leakage it would *potentially* be more sensitive to a chaotic response. In Souza *et al* [21] we applied the Welch power spectrum to subjects with diabetes. These then gave us the standard spectral Entropy and spectral Detrended fluctuation analysis (sDFA). Further studies on malnutrition [24], youth obesity [25] and a study on attention deficit hyperactivity disorder (ADHD) [26] applied the MTM power spectra throughout. These were referred to as *high spectral* Entropy and *high spectral* Detrended fluctuation analysis (*hs*DFA). During all studies we applied the MTM power spectrum to generate the third parameter spectral Multi-Taper Method (sMTM) [4]. This quantifies the extent of broadband noise in the system associated with increasing chaotic response. This parameter remains unchanged throughout all the subsequent analysis.

When we compute power spectra via Welch's method the parameters are set at: (i) sampling frequency of 2Hz, (ii) zero overlap, (iii) a Hamming window and the number of discrete Fourier transform (DFT) point to use in the power spectral density (PSD) estimate is the greater of 256 or the next power of two greater than the length of the segments, and (iv) there is no detrending. These were calculated in the study by Souza *et al* [21].

To compute the MTM, the parameters are set as the following: (i) sampling frequency of 1Hz; (ii) time bandwidth for the discrete prolate spheroidal sequences (DPSS) often referred to as slepian sequences [27] is 3; (iii) a discrete Fourier transform (DFT) length of 256; (iv) Thomson's *adaptive* nonlinear combination method to combine individual spectral estimates is applied. These were applied in studies on youth obesity [25], malnutrition [24] and ADHD [26].

The Periodogram power spectral density estimate is a nonparametric estimate of a wide-sense stationary random process using a rectangular window. The number of points in the discrete Fourier transform (DFT) is a maximum of 256 or the next power of two greater than the signal length.

For Covariance, Burg and Yule-Walker methods the order is of the autoregressive model (AR) used to produce the power spectra density estimate and is set to 4. A default discrete Fourier transform (DFT) length of 256 is applied.

In this study, when computing spectral Entropy and sDFA we enforce six different power spectra (Welch, MTM, Covariance, Burg, Yule-Walker and Periodogram) to give six variants of these parameters. There are seven different permutations of three chaotic global parameters. All three chaotic global values have equal weighting of unity. The Chaotic Forward Parameter (CFP) enables different combinations of 'chaotic globals' to be applied to ensure optimum chaotic response - tested later by multivariate analysis. It is expected that the CFP which applies all three should be the most significant and robust since it takes the information and processes it in three different

ways. It is assumed that the CFP1 which is applied to the MTM power spectrum should be the best overall statistically. It is adaptive, nonlinear and intrinsically promotes reduced spectral leakage.

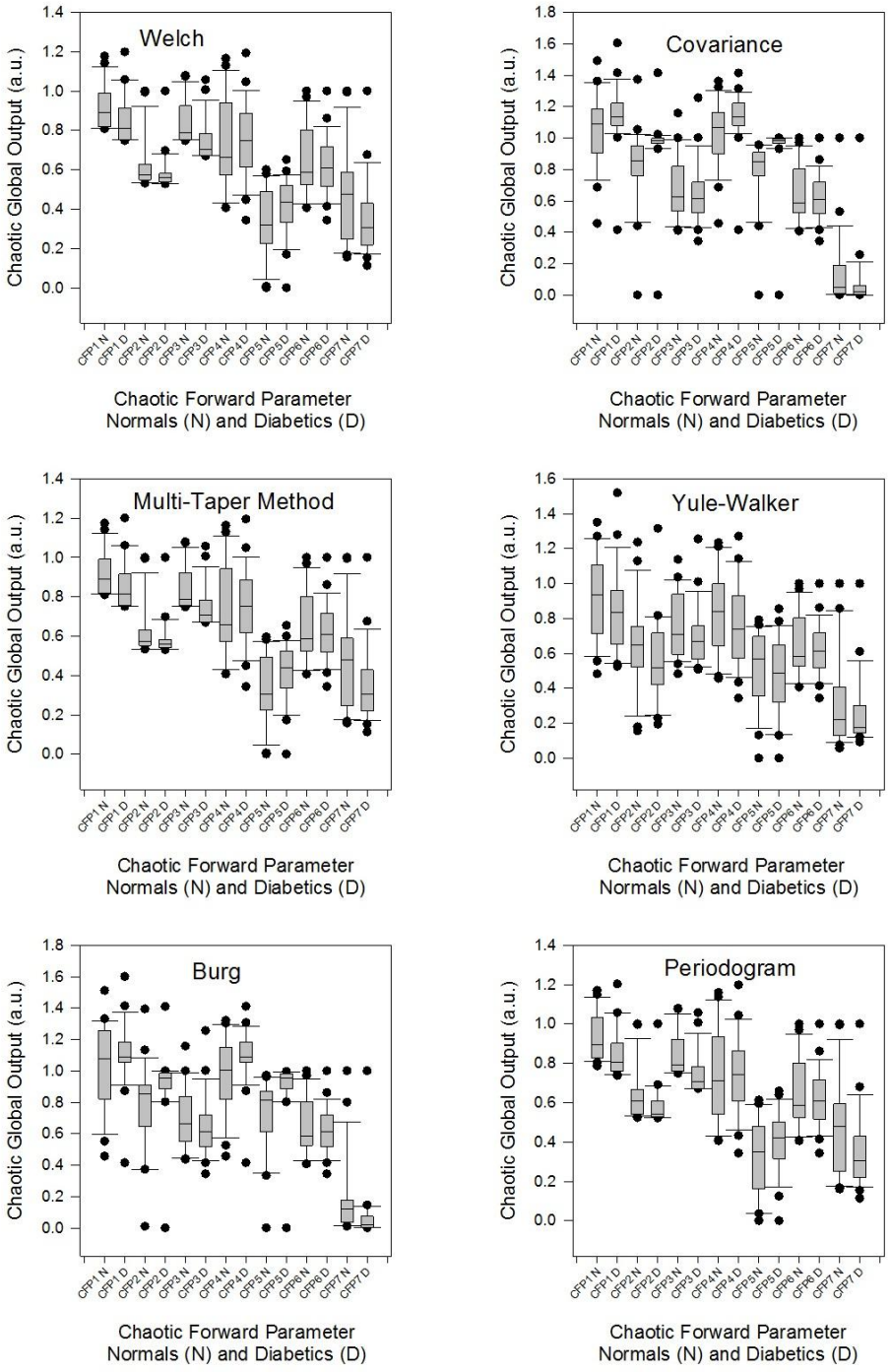

Figure 1. *The boxplots of the seven combinations of chaotic forward parameters (CFP 1 to 7) for the six power spectra density (PSD) estimates (Welch, MTM, Burg, Covariance, Yule-Walker and Periodogram) of 1000 RR intervals in normal subjects (CFPx N) and diabetic subjects (CFPx D). The point closest to the zero is the minimum and the point farthest away is the maximum. The point next closest to the zero is the 5th percentile and the point next farthest away is the 95th percentile. The boundary of the box closest to zero indicates the 25th percentile, a line within the box marks the median (not the mean), and the boundary of the box farthest from zero indicates the 75th percentile. The difference between these points is the inter-quartile range (IQR). Whiskers (or error bars) above and below the box indicate the 90th and 10th percentiles respectively.*

Statistical Analyses

Parametric statistics accept that the data 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 applied the Anderson-Darling [28] and Lilliefors [29] tests. The Anderson-Darling test for normality applies an empirical cumulative distribution function. The Lilliefors test is useful in studies such as these with small sample sizes. Here, the results were inconclusive so we cannot assert that the observations follow either a normal or non-normal distribution. Therefore we applied both parametric and nonparametric tests of significance. These are the one-way analysis of variance (ANOVA1) [30] and the Kruskal-Wallis [31] tests of significance, respectively. We illustrate the results as boxplots, in Figure 1 and statistically in the Table 1.

Table 1. Table of results for the mean and standard deviation of the chaotic responses CFP 1 to 7 derived by six different power spectra (Welch, MTM, Burg, Covariance, Yule-Walker & Periodogram) for those normal subjects (n=23) and those with diabetes mellitus (n=23). We also compute the significance (p-value) by parametric and nonparametric techniques: One way Analysis of Variance (ANOVA1) and Kruskal-Wallis tests of significance respectively. We mark those with significances $p<0.05$ with (*) and those with $p<0.01$ with (**).

Power Spectra Applied	Chaotic Forward Parameter	Mean ± SD Normal (n=23)	Mean ± SD Diabetic (n=23)	ANOVA1 (p-value)	Kruskal-Wallis (p-value)
Welch Power Spectrum	CFP1	0.9212 ± 0.1197	0.8590 ± 0.1202	0.0859	0.0288*
	CFP2	0.6332 ± 0.1365	0.5869 ± 0.0999	0.1962	0.1040
	CFP3	0.8465 ± 0.1074	0.7464 ± 0.1043	0.0025**	0.0002**
	CFP4	0.7279 ± 0.2251	0.7378 ± 0.1985	0.8746	0.8347
	CFP5	0.3255 ± 0.1734	0.4041 ± 0.1481	0.1057	0.0994
	CFP6	0.6440 ± 0.1735	0.6133 ± 0.1504	0.5243	0.6445
	CFP7	0.4760 ± 0.2451	0.3642 ± 0.1969	0.0954	0.1040
Multi-Taper Method (MTM) Power Spectrum	CFP1	0.9217 ± 0.1194	0.8603 ± 0.1202	0.0893	0.0273*
	CFP2	0.6340 ± 0.1362	0.5889 ± 0.0995	0.2066	0.1471
	CFP3	0.8467 ± 0.1072	0.7463 ± 0.1043	0.0024**	0.0002**
	CFP4	0.7283 ± 0.2248	0.7394 ± 0.1985	0.8597	0.8347
	CFP5	0.3268 ± 0.1725	0.4071 ± 0.1480	0.0973	0.1040
	CFP6	0.6440 ± 0.1735	0.6133 ± 0.1504	0.5243	0.6445
	CFP7	0.4765 ± 0.2248	0.3641 ± 0.1967	0.0931	0.1040
Burg Power Spectrum	CFP1	1.0317 ± 0.2653	1.1112 ± 0.2155	0.2706	0.4100
	CFP2	0.7823 ± 0.2821	0.9112 ± 0.2311	0.0971	0.0119**
	CFP3	0.7096 ± 0.1976	0.6373 ± 0.1999	0.2234	0.1381
	CFP4	0.9893 ± 0.2407	1.0946 ± 0.1895	0.1064	0.1064
	CFP5	0.7326 ± 0.2374	0.8915 ± 0.2044	0.0191*	0.0002**
	CFP6	0.6440 ± 0.1735	0.6133 ± 0.1504	0.5243	0.6445
	CFP7	0.1901 ± 0.2532	0.0801 ± 0.2049	0.1126	0.0023**
Covariance Power Spectrum	CFP1	1.0530 ± 0.2349	1.1490 ± 0.2052	0.1472	0.1017
	CFP2	0.8078 ± 0.2619	0.9555 ± 0.2282	0.0475*	0.0001**
	CFP3	0.6888 ± 0.1986	0.6392 ± 0.1986	0.4021	0.3283
	CFP4	1.0249 ± 0.2109	1.1316 ± 0.1811	0.0725	0.0243*
	CFP5	0.7755 ± 0. 2242	0.9349 ± 0.2048	0.0156*	<0.0001**
	CFP6	0.6440 ± 0.1735	0.6133 ± 0.1504	0.5243	0.6445
	CFP7	0.1402 ± 0.2263	0.0850 ± 0.2080	0.3937	0.1410

Table 1. *Continued.*

Power Spectra Applied	Chaotic Forward Parameter	Mean ± SD Normal (n=23)	Mean ± SD Diabetic (n=23)	ANOVA1 (p-value)	Kruskal-Wallis (p-value)
Yule-Walker Power Spectrum	CFP1	0.9307 ± 0.2448	0.8432 ± 0.2491	0.2360	0.1912
	CFP2	0.6453 ± 0.2581	0.5624 ± 0.2427	0.2681	0.1838
	CFP3	0.7570 ± 0.1791	0.6917 ± 0.1737	0.2161	0.1912
	CFP4	0.8430 ± 0.2347	0.7794 ± 0.2362	0.3643	0.4100
	CFP5	0.5257 ± 0.2135	0.4632 ± 0.2252	0.3397	0.2533
	CFP6	0.6440 ± 0.1735	0.6133 ± 0.1504	0.5243	0.6445
	CFP7	0.3113 ± 0.2572	0.2654 ± 0.2022	0.5047	0.6445
Periodogram Power Spectrum	CFP1	0.9298 ± 0.1205	0.8595 ± 0.1246	0.0581	0.0161*
	CFP2	0.6458 ± 0.1368	0.5878 ± 0.1042	0.1127	0.0265*
	CFP3	0.8484 ± 0.1068	0.7472 ± 0.1040	0.0022**	0.0002**
	CFP4	0.7356 ± 0.2291	0.7370 ± 0.2033	0.9833	0.8176
	CFP5	0.3364 ± 0.1904	0.4011 ± 0.1586	0.2171	0.3228
	CFP6	0.6440 ± 0.1735	0.6133 ± 0.1504	0.5243	0.6445
	CFP7	0.4792 ± 0.2453	0.3659 ± 0.1968	0.0912	0.1040

Principal Component Analysis (PCA) [32,33] is a multivariate statistical technique where random observations are transformed into a smaller set of uncorrelated variables termed Principal Components (PCs). The term component refers to a linear transformation that selects a variable system for the data set such that the greatest variance of the data lies on the first axis; the first principal component, (PC1), with the second greatest variance on the second axis (PC2). These components are uncorrelated since in sample space they are orthogonal (or perpendicular) to each other.

We assess PCA when phenomena cannot be directly observed. Especially, when the objective is to identify and operate with underlying latent factors rather than the observed data. They are useful when there is an excess of observations and dimensions with the need to reduce them to a smaller number of factors. It is the most widely applied statistical computation for dimensionality reduction. The cumulative influences are described as a percentage. If the PCs account for the majority of influence in the first few components we achieve a steep scree plot.

Results

We have the values of CFP for seven groups for 23 subjects who are diabetic; hence a grid of 7 by 23 to be assessed for each of the six power spectra. From Table 1 we observe that the derivatives from the Welch and MTM power spectrum respond in a very similar manner. CFP1 and CFP3 are highly significant. CFP1 has a $p \approx 0.03$ for the Kruskal-Wallis test of significance for both power spectra and CFP3 has a $p \leq 0.01$ for the Kruskal-Wallis and ANOVA1 tests of significance. In both circumstances, the diabetic subjects have lower mean values for the CFP1 and CFP3. This is to be expected for dynamical diseases. The Welch and MTM power spectra also respond similarly with respect to the multivariate analytical technique PCA.

For the Welch power spectra CFP1 has the First Principal Component (PC1) (0.256) and the Second Principal Component (PC2) (-0.520); whereas, CFP3 has the PC1 (0.048) and the PC2 (-0.610). Only the first two components need be considered due to the steep scree plot. The cumulative influence as a percentage is 61.9% for the PC1 and 99.8% for the cumulative total of the PC1 and PC2. So, CFP1 which applies all

three chaotic globals techniques is the best and most robust overall combination with regard to influencing the correct outcome.

For MTM power spectra CFP1 has the PC1 (0.257) and the PC2 Component (-0.518); whereas, CFP3 has the PC1 (0.049) and the PC2 (-0.609). Only the first two components need be considered due to the equally steep scree plot. The cumulative influences are exactly the same as with the Welch power spectra above. So, CFP1 which applies all three chaotic globals techniques is the preferred overall combination with regard to influencing the correct outcome..

Regarding the Burg power spectrum CFP2, CFP5 and CFP7 are highly significant at the level of $p \leq 0.01$ for the Kruskal-Wallis test. Yet, in the case of CFP2 and CFP5 the diabetics subjects mean values are greater than the normal group which is unexpected and so can be disregarded. CFP7 decreases for the diabetic subjects with $p \leq 0.01$ for the Kruskal-Wallis test. It is however insignificant for the ANOVA1 tests with a p-value of 0.1126. Also, it is a single parameter based on spectral Entropy alone so is not principally robust as would be the case with CFP1. Thus, these results need not be considered further.

Concerning the Covariance power spectrum CFP2 is important at the level of $p \leq 0.01$ for the Kruskal-Wallis test of significance and $p \approx 0.05$ for ANOVA1. CFP4 is significant at the level of $p \leq 0.05$ for the Kruskal-Wallis test of significance, and CFP5 is significant at the level of $p \leq 0.01$ for the Kruskal-Wallis test of significance but for the ANOVA1 the p-value is less significant at 0.0156. Though, in all significant cases the diabetics have mean values which advocate that they have greater chaotic response than the normal groups. This is not to be expected since the dynamical diseases are expected to correlate with a reduced chaotic response. Consequently, these results need not considering further.

Regarding the Yule-Walker power spectrum there are no combinations of chaotic global parameters (CFP1 to CFP7) which are significant. So, these results are not further considered.

For the Periodogram power spectrum the CFP1, CFP2 and CFP3 permutations of chaotic global parameters are all significant. In all three cases the diabetics have lower values for the combination of chaotic global parameters which is expected. CFP1 and CFP2 are significant at the level of $p \leq 0.05$ for the Kruskal-Wallis test of significance. CFP3 is significant at the level of $p \leq 0.01$ for both ANOVA1 and Kruskal-Wallis tests of significance.

Regarding the Periodogram power spectra, CFP1 has the PC1 (0.291) and the PC2 (-0.491); whereas, CFP2 has the PC1 (-0.147) and the PC2 (-0.576) and, CFP3 has the PC1 (0.080) and the PC2 (-0.600). Only the first two components need be considered due to the steep scree plot. The cumulative influence as a percentage is 61.0% for the PC1 and 98.7% for the cumulative total of the PC1 and PC2. So, CFP1 which applies all three chaotic globals techniques is the best overall combination with regard to influencing the correct outcome.

Discussions

We can recognize from the results above that the most robust parameters throughout are CFP1 and CFP3. This is the case for three of the power spectra – Welch, MTM and Periodogram all predicated on the Fast Fourier Transform, and all are non-parametric methods. It is expected that CFP1 would be the most statistically robust parameter since it applies three parameters as an alternative to two provided with CFP3. It is noteworthy that the Welch and MTM power spectra perform very similarly, as would be

expected. The Periodgram performed more significantly on the statistical tests, but less influential on the multivariate analysis. A Periodogram spectrum can give consistent results with higher noise levels than the other two. It is the least sophisticated algorithm applied here [12].

For the other three power spectra, all are parametric methods – Burg, Covariance and Yule-Walker and the results are largely insignificant. The order of the power spectra has little influence over the results. Yule-Walker derivatives have no significant values by parametric or non-parametric statistical tests; therefore, we do not need to perform any multivariate analysis. For the Burg power spectrum the only valid result is CFP7 which is a single entity and as such not robust and need not be considered further. For Covariance power spectrum in all significant cases the diabetics have mean values which suggest that they have greater chaotic response than the normal groups. This is not to be expected since optimally functioning physiological systems have higher values for chaotic response. So, the Covariance technique can be rejected.

Returning to MTM we call these derivatives *high spectral* Entropy and *high spectral* Detrended fluctuation analysis (*hs*DFA) and they do *slightly* outperform those derived from the Welch power spectrum. However, the MTM power spectrum excels with regards to the various parameters which define the spectrum. For instance, the time bandwidth for the DPSS can be adjusted and Thomson's 'adaptive' nonlinear combination method to combine individual spectral estimates can be attuned to the 'eigenvalue' or 'unity' settings. This flexiblity has the potential to increase the significance of CFP1 and CFP3 derived from MTM power spectra and could form the basis of another study. It would also be statistically favourable to have larger datasets for both normal and diabetic subjects. If the time-series were longer this should enhance statistical significances.

Conclusions

We have derived two robust and important functions CFP1 and CFP3 which can compute short time-series of HRV and deduce which time-series is from a diabetic patient and which from the normal subjects. We have also derived two of the chaotic global parameters by six different power spectra. On the basis of three statistical tests we determine that the Welch and MTM power spectra provide the most significant results with Periodgram perfoming better on the ANOVA1 and Kruskal-Wallis tests, but slightly less influential on the multivariate analysis. Yule-Walker, Burg and Covariance power spectra perform much worse when applied to the two chaotic globals stated. Therefore we can assume that the optimum parameters to apply are those wholly derived from the MTM power spectrum. They match those of the Welch power spectrum but outperform it with the additional flexiblity performed by DPSS and Thomson's nonlinear combination methods. Therefore the optimum parameter is the CFP1 a function of *high spectral* Entropy, *high spectral* Detrended Fluctuation Analysis (*hs*DFA) and spectra Multi-Taper Method (sMTM).

By applying these algorithms to short sections of RR-interval data it should be possible to achieve a diagnosis and provide the necessary treatment earlier.

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