NONLINEAR REGULATION OF CARDIAC AUTONOMIC MODULATION IN OBESE YOUTHS: INTERPOLATION OF ULTRA-SHORT TIME-SERIES

Novel nonlinear HRV analysis in obese youths

David M. Garner[1], Franciele M. Vanderlei[2], Vitor E. Valenti*[3], Luiz Carlos M. Vanderlei[2]

[1]Cardiorespiratory Research Group, Department of Biological and Medical Sciences,
Faculty of Health and Life Sciences, Oxford Brookes University,
Headington Campus, Gipsy Lane, Oxford OX3 0BP, United Kingdom

[2]Department of Physiotherapy, Sao Paulo State University, UNESP, Presidente Prudente,
Sao Paulo, Brazil

[3]Autonomic Nervous System Center, Sao Paulo State University, UNESP, Marilia, SP, Brazil.

***Corresponding author:**

Sao Paulo State University

Rua Roberto Simonsen, 305 - Centro Educacional - P. Prudente/SP - CEP 19060-900

Brazil

Phone: (18) 3229-5388

E-mail: vitor.valenti@unesp.br

ABSTRACT

BACKGROUND: In this study we applied ultra-short time-series of RR-intervals to evaluate heart rate variability (HRV) through default chaotic global techniques with the purpose of discriminating obese youths from non-obese youth subjects. **METHOD:** Chaotic global analysis of the RR-intervals from the electrocardiogram and pre-processing adjustments were undertaken. The effect of cubic spline interpolations were assessed whilst the spectral parameters remained fixed. Exactly, 125 RR-intervals of data were recorded. **RESULTS:** CFP1, CFP3 and CFP6 were the only significant combinations of chaotic globals when the standard conditions were enforced and at the level $p<0.01$, (or <1%). These significances were acheived via Kruskal-Wallis and Cohen's d_s effects sizes tests of significance after Anderson-Darling and Lilliefors statistical tests indicated non-normal distributions in the majority of cases. Adjustments of the cubic spline interpolation from 1Hz to 13Hz were revealed to be inconsequential when measured by Kruskal-Wallis and Cohen's d_s, regarding the outcome between the two datasets. **CONCLUSION:** Chaotic global analysis was offered as a robust technique to distinguish autonomic dysfunction in obese youths. It can discriminate the two different groups using ultra-short data lengths and no cubic spline interpolations need be applied.

Keywords: Obese Youths; Ultra-Short Time-Series; Cubic Spline Interpolation; Chaotic Globals.

INTRODUCTION

Heart rate variability (HRV) is an important sign for diagnosing cardiac pathological states[1]. Mathematical algorithms founded on nonlinear dynamics are useful when analyzing these conditions. They are vital when developing new methods to reach an early differential diagnosis about cardiovascular disease conditions[2]. The sympathetic and parasympathetic nervous systems' connections have been demonstrated to influence HRV by nonlinear neurological cross-talk. HRV is a simple, inexpensive and non-invasive way of monitoring the cardiac branches of the Autonomic Nervous System (ANS). Other procedures can be unresponsive such as with Sympathetic Skin Response[3] or, too complicated and highly-priced as with Quantitative Pupillography[4].

The beat of electrocardiographic (ECG) RR-intervals derived from the PQRST-motif can pulsate in an irregular and often chaotic manner[5, 6]. This has been previously undertaken[7, 8], but with much longer data sets (1000 RR-intervals) and without judging the potential consequences of cubic spline interpolations[9]. These chaotic global metrics are especially sensitive to unpredictabilites. This is predominant when compared with those based on linear descriptive statistics, conventional nonlinear or geometric routines. The larger the response, usually the healthier the subjects' physiological status. Less chaos can typically be interpreted as a mathematical marker for dynamical disease states, in particular[10]. Dynamical diseases are characterized by unexpected instabilities in the qualitative dynamics of physiological processes. This leads to irregular dynamics and then pathological states. So, there is a physiological connection between nonlinear dynamics (or complexity theory) and clinical medicine[11]. This method is valuable to the clinical team to identify subtle changes in the ANS, and to predict the risk of problems.

Such computations are advantageous when assessing surgical patients[12] principally anaesthetized[13] or unable to communicate distress such as in sleep apnea patients[14] or those experiencing "air hunger"[15, 16]. However, the use of ultra-short time-series of RR-intervals to evaluate heart rate variability (HRV) through default chaotic global techniques for evaluation of health conditions, are unknown in the literature.

Through the RR-intervals we compute three chaotic global parameters and seven groupings to determine the control from the experimental time-series. We assumed that these subjects from obese youths' datasets presented autonomic alterations that can be observed with the proposed analyzes.

METHODS

Patient Selection and assessments were exactly as with the studies by Vanderlei *et al*[7] and Garner *et al*[8]. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All volunteers signed a consent letter and was informed of the procedures and objectives of the study. The study's procedures were all approved by the Research Ethics Committee of UNESP (Number Protocol No. 11/2011).

Chaotic Globals & Chaotic Forward Parameters

There are three types of chaotic global parameter. They are characterized as *high spectral* Entropy (*hs*Entropy)[7], *high spectral* Detrended Fluctuation Analysis (*hs*DFA)[7] and Spectral Multi-Taper Method (sMTM)[17]. All are functions of the Multi-Taper Method (MTM) power spectrum[18]. As such, MTM is a form of power spectrum that has been revealed to be beneficial for spectral estimation[19]. Its major advantage is the minimization of spectral leakage. Functions described as discrete prolate spheroidal sequences (DPSS); often referred to as Slepian Sequences[20] are a set of functions which optimize their windows. Regarding *hs*Entropy, Shannon entropy[21] is applied directly onto the MTM power spectrum. Whereas with *hs*DFA, Peng's (1995) algorithm the Detrended Fluctuation Analysis (DFA)[22] is applied directly onto an identical MTM power spectrum. Spectral Multi-Taper Method (sMTM)[17] is dependent on elevated broadband noise intensities generated in MTM power spectra by irregular and often chaotic signals. When broadband noise is increased significantly during an elevated chaotic response the area beneath the power spectrum increases. sMTM is the area between this power spectrum and the baseline.

Chaotic Forward Parameters 1 to 7 (CFP1 to CFP7)[19] are enforced on the ECGs RR-intervals for the non-obese and obese youths' subjects. *hs*DFA responds to levels of chaos contrariwise to the others, so we deduct its value from unity. Weightings of unity are stated here for each of the three chaotic global parameters.

There are seven non-trivial combinations of three chaotic global values[23]. It is anticipated CFP1 which applies all three should be the most statistically robust. This for the reason it takes the information and processes it in three different ways. The summation of the three would be expected to deviate greater than single or double permutations. The potential danger is since we are only computing spectral components - phase information is lost.

Principal Component Analysis

Principal Component Analysis (PCA)[24, 25] is a multivariate statistical technique for analyzing the complexity of high-dimensional data sets. PCA is useful when sources of variability in the data need to be explained or reducing the complexity of the data and through this assess the data with lesser dimensions. The primary aim of PCA is to represent the data with fewer variables whilst sustaining the majority of the total variance. There are two major properties of the PCA. First, the technique is non-parametric so no prior knowledge can be incorporated. And then secondly, PCA data reduction often incurs a loss of information.

Next, there are the assumptions of the technique. Initially linearity, this accepts the data set to be linear combinations of the variables. Then, the importance of mean and covariance, hence no assurance that the direction of maximum variance will contain good discriminative features. And finally, large variance has the most important dynamics and the lowest corresponding to noise.

When interpreting the PCA four points should be considered. First, the higher the component loadings the more important that the variable is to the component. Second, positive and negative loadings are interpreted as mixed. Third, the specific sign of these mixed loadings is unimportant. Finally, the rotated component matrix is vital.

Effect Sizes by Cohen's d_s

Cohen's *d* [26, 27] generally, denotes the entire group termed effect sizes. To quantify the magnitude of difference between protocols for significant differences, the effect size was estimated through a sub-group Cohen's d_s [28]. Cohen's d_s represent the standardized mean difference of an effect. It can be used to calculate effects across studies even when the dependent variables are measured in alternative ways or even when completely different measures are used. It varies from zero to infinity which may be positive or negative. However, Cohen refers to the standardized mean difference between two groups of independent observations for the appropriate *sample* as d_s.

In the equation for Cohen's d_s (see below), the numerator is the difference between the appropriate means of two groups of observations. The denominator is the pooled standard deviation. These differences are squared to prevent the positive and negative values cancelling each other out. Then, they are summed. This is then divided by the number of observations minus one (referred to as Bessel's correction) for bias in the estimation of the population variance, and then the square root of this is taken.

$$Cohen's\, d_s = \frac{\overline{X}_1 - \overline{X}_2}{\sqrt{\frac{(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2}{n_1 + n_2 - 2}}}$$

Regarding these effect sizes d_s the following describes the magnitude for the values according to Sawilowsky[29]; 0.01 > very small effect; 0.20 > small effect; 0.50 > medium effect; 0.80 > large effect; 1.20 > very large effect, and finally 2.00 > a huge effect size.

Cubic-spline Interpolation

Subsequently, we assessed the importance of pre-processing techniques on the results obtained through chaotic global algorithms. Again we compare the chaotic global values for CFP1 to CFP7. Time-series constructed from the RR-interval tachograms are not equidistantly sampled. This has to be justified before frequency-domain analysis.

Primarily, we can decide to assume equidistant sampling[30] and compute the power spectrum directly from the tachogram of RR-intervals. This is the technique widely adopted up-til-now by previous studies on chaotic globals with obese children[31], ADHD[23], type 1 diabetes mellitus[32] and flexible-pole physical therapy shoulder rehabilitation[33] amongst others. The RR-intervals are therefore a function of the beat number. Yet, this could cause a distortion in the spectrum[34] and the spectrum must be considered a function of cycles per beat rather than of frequency[35]. Incidentally, a Lomb power spectrum[36] could also be used as an alternative power spectrum specifically for unequally spaced data. Nevertheless, here it is not relevant so not discussed further.

A completely different approach here is to enforce a cubic spline interpolation[37] to convert the nonequidistantly sampled RR-tachogram into an equidistantly sampled time series[38]. So we performed a cubic spline interpolation on the RR-interval tachogram. We accomplished this at the levels 1Hz to 13Hz. This covers most relevant scenarios in HRV analysis. Kubios HRV®[39] software offers a default option of 4Hz. It is important to grasp that the interpolation frequency will effect the number of data points in the time-series. A frequency of 4Hz for example will elevate the number of RR-intervals from 125 (1Hz) to 500 (4Hz).

Following the cubic spline interpolation, the chaotic global algorithms parameters are fixed.

Throughout the enforcement of the cubic spline interpolations the MTM default parameters were set to the following. Thomson's setting to 'adaptive', sampling frequency to 1Hz, FFT length of 256 and the DPSS to 3.

RESULTS

Table 1 presents data regarding (sex, age, mass and body mass index-BMI).

Statistics illustrate that there is a wide variation in both the mean values and standard deviation for both non-obese and obese youths. Here, we are assessing ultra-short time-series (125 RR-intervals). Previously, in studies of obese youths[7, 8], 1000 RR-intervals were evaluated. The chaotic global algorithms in this study compute a significant statistical result ($p<0.01$, <1%) for three of the seven combinations (See Table 2 & Figure 1). These are combinations CFP1, CFP3 and CFP6 as with the former study but, here with an eight times shorter time-series. In all three cases there is a significant increase in chaotic response when comparing non-obese to obese youth subjects.

The non-parametric Kruskal-Wallis test of significance was calculated. This was since the distributions were revealed to be non-normal in the majority of cases, determined by the Anderson-Darling[40] and Lilliefors[41] statistical tests. Effect sizes by Cohen's d_s [26-28] were also calculated as there was a wider range of values.

With regards to the multivariate statistical analysis by PCA (See Figure 2). Only the first two components need be considered by reason of a moderately steep scree plot. The cumulative influence as a percentage is 66.8% for Principal Component One (PC1) and 99.8% for the cumulative total of the PC1 and Principal Component Two (PC2). PC2 has an individual influence of 33.0%. From Figure 2 it is evident that metrics CFP3 and CFP1 are the most influencial on the basis of the first two components. This is to be expected as CFP1 is usually the most statistically robust and CFP3 the most statistically significant.

The effect of cubic spline interpolation between 1Hz and 13Hz increasing the length of the time-series by interpolation (rather than by recording longer time-series in the laboratory) is negligible. This is for CFP1, CFP3 and CFP6 via both Kruskal-Wallis and effect sizes by Cohen's d_s test of significances as illustrated in Table 3. Of those that are significant with default chaotic global values. It is apparent that the Cohen's d_s are most significant for CFP6 ($d_s \approx -0.76$) then CFP3 ($d_s \approx -0.64$), and least so for CFP1 ($d_s \approx -0.54$). The negative sign indicates an increase from non-obese to obese youths. The Kruskal-Wallis tests indicate significances of $p<0.01$ for all, hence the use of Cohen's d_s which has a wider range of values and so is more useful to discriminate between the interpolations.

DISCUSSION

It is unclear why different algorithms behave in alternative ways for heart rate autonomic control. Consequently, our study aimed to assess a new approach to detect autonomic dysfunction in obese youths based on the nonlinear dynamics from the non-periodic RR-intervals oscillations. As a chief outcome, chaotic global techniques applied for HRV analysis were able to identify cardiac autonomic dysfunction in a sample of obese youths and using an ultra-short time series of 125 RR-intervals.

HRV has received much attention by reason of its simple workability. Data can be collected by a one-channel ECG or a pulse watch. Then, these RR-intervals can be processed by Kubios HRV® software[39]. Previously, Task Force in 1996 published directives in order to regulate HRV analysis using linear methods in the time and frequency domains[38].

Nonlinear analysis of HRV was specified to provide information about the scaling, quality and correlation properties of the time series. There are countless nonlinear techniques; some based on Approximate, Sample, Shannon, Renyi and Tsallis Entropies[42] or, Higuchi and Katz's fractal dimensions[43] and specifically the novel chaotic global metrics[17] investigated in this study. Linear methods were intended to compute HRVs extent. Complex algorithms to assess the level of chaotic response of HRV is suggested to detect autonomic changes that linear methods are unable to identify[44]. This is the key advantage of the nonlinear techniques.

Globally chaotic methods have hitherto been applied to RR-intervals in obese children[31] or obese youths[7] and, malnourished children[45]. There have, thus far, been no studies enforcing the cubic spline interpolation on chaotic global methods. Few studies have assessed ultra-short time-series of 125 RR-intervals with any metric. The previous studies[7, 23] have assessed time-series eight times lengthier. Historically, metrics assessing data required 24-hour Holter ECG recordings[46] to make considerations. This was severely reduced when the spectrally involved chaotic globals were introduced[17]. Until now, even chaotic globals had not been tested on 125 RR-intervals. Ultimately, the results are favorable with three metrics (CFP1, CFP3 and CFP6) all discriminated from the controls at the level $p<0.01$ (or, <1%) on ultra-short time-series.

Some limitations from our study need highlighting. We evaluated a small sample, yet, statistical analysis provided significance. The sample was comprised of only Brazilian subjects. Thus, we should be cautious when interpreting such data in countries from different continents. We did not obtain information regarding body fat percentage, lean mass, inflammatory markers and oxidative stress. Further studies are encouraged to evaluate the correlations between the mentioned variables and chaotic global analysis. Different autonomic approaches for example, electroneuromycrography, baroreflex function and skin response were not investigated, as our emphasis was chaotic global analysis applied to RR-intervals -- a relatively low cost technique.

Our study presents important findings for clinical practice and procedures. ICUs and physicians are interested in predicting the risk for physiological complications. Comprehension of biological signals through nonlinear analysis of HRV is a significant issue for an appropriate program of care. We revealed that chaotic globals applied to ultra-short time-series of RR-intervals is sensitive to differentiate autonomic impairment of obese youths from non-obese youth subjects. Yet, cubic spline interpolations have only trivial effects. Therefore we can accept that cubic spline interpolation is unnecessary and, shorter than usual time-series are adequate to make decisions about cardiac autonomic dysfunction in obese youths. By using shorter time-series computations, they are less processor intensive and can be calculated faster which is advantageous in an ICU setting where decisions need to be made quickly. Nonetheless, it is important to realize though this may not be the case with other experimental groups which must be assessed individually on their merits alone.

CONCLUSION

The three chaotic global techniques (CFP1, CFP3 and CFP6) applied to an ultra-short time-series of 125 RR-intervals robustly detected HRV deviations in obese youth subjects. Extensive interpolation of time-series made statistically insignificant effects by two statistical tests, and so was unneccessary. Yet, these three techniques were able to identify autonomic dysfunction in obese youth subjects and accordingly discriminate between these two groups.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

ETHICAL STANDARDS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All volunteers signed a consent letter and was informed of the procedures and objectives of the study. The study's procedures were all approved by the Research Ethics Committee of UNESP (Number Protocol No. 11/2011).

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Table 1: Sex, mean values followed by their respective standard deviations of age, mass and BMI.

Variable	Obese	Control
Sex (female)	20	21
Age (years)	20.45 ± 1.57	20.70 ± 1.39
Mass (kg)	102.30 ± 20.82	62.89 ± 10.47
BMI (Kg/m^2)	34.67 ± 3.87	21.91 ± 1.86

Legend: kg: kilogram; m: meters; BMI: body mass index.

Table 2: Mean values and standard deviations for the chaotic forward parameters CFP1 to CFP7 which are non-dimensional values; for the non-obese and obese youth subjects with 125 RR-intervals. Kruskal-Wallis test of significance was computed as distributions were mainly non-normal by Anderson-Darling and Lilliefors tests of normality. Cohen's d_s effects sizes were also calculated where a negative value signifies an increase in chaotic response from non-obese to obese youth and a positive value the opposite response.

Chaotic Global CFPx	**Mean ± S.D. Normal (n=43)**	**Mean ± S.D. Youth Obese (n=43)**	**Kruskal-Wallis (p-value)**	**Cohen's d_s Effect Sizes**
CFP1	0.8080 ± 0.1154	0.8726 ± 0.1225	0.001	-0.542
CFP2	0.5995 ± 0.1036	0.5828 ± 0.0795	0.723	0.181
CFP3	0.6960 ± 0.1080	0.7613 ± 0.0957	<0.001	-0.640
CFP4	0.6536 ± 0.1994	0.7611 ± 0.1986	0.015	-0.540
CFP5	0.3819 ± 0.1574	0.4106 ± 0.1394	0.364	-0.193
CFP6	0.5254 ± 0.1428	0.6382 ± 0.1532	0.001	-0.761
CFP7	0.3965 ± 0.2090	0.3571 ± 0.1775	0.374	0.203

Table 3: CFP1, CFP3 & CFP6 (non-dimensional values) and their test of significances by Kruskal-Wallis and Effect sizes Cohen's d_s for the non-obese compared to obese youth subjects. DPSS is set to 3 and length of time-series is starts at 125 RR-intervals for an interpolation rate of 1Hz. So, this increases to 250 RR-intervals with an interpolation rate of 2Hz and so on. To calculate the MTM, settings are fixed as follows: sampling frequency of 1Hz, 256 for FFT length and Thomson's 'adaptive' nonlinear combination method.

Interpolation Rate (Hz)	**Kruskal-Wallis Test**			**Effect Sizes by Cohen's d_s**		
	CFP1	**CFP3**	**CFP6**	**CFP1**	**CFP3**	**CFP6**
1	0.001	<0.001	0.001	-0.543	-0.640	-0.761
2	0.001	<0.001	0.001	-0.545	-0.639	-0.760
3	0.001	<0.001	0.001	-0.546	-0.640	-0.761
4	0.001	<0.001	0.001	-0.547	-0.639	-0.760
5	0.001	<0.001	0.001	-0.546	-0.640	-0.760
6	0.001	<0.001	0.001	-0.547	-0.640	-0.760
7	0.001	<0.001	0.001	-0.547	-0.639	-0.759
8	0.001	<0.001	0.001	-0.549	-0.639	-0.760
9	0.001	<0.001	0.001	-0.548	-0.640	-0.760
10	0.001	<0.001	0.001	-0.548	-0.639	-0.760
11	0.001	<0.001	0.001	-0.548	-0.640	-0.760
12	0.001	<0.001	0.001	-0.548	-0.640	-0.760
13	0.001	<0.001	0.001	-0.548	-0.639	-0.760

FIGURE LEGENDS

Figure 1: The boxplots for CFP1 to CFP7 aimed at non-obese and the obese youth subjects (n=43) with 125 RR-intervals. 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.

Figure 2: The plot illustrates the component loadings CFP1 to CFP7 for the 125 RR-intervals of 43 obese youth subjects' described above with a cubic spline interpolation of 1Hz. The CFP values are deduced by using the MTM spectra throughout. The properties of the MTM spectra are as follows: Sampling frequency 1Hz, DPSS of 3, FFT length of 256 and Thomson's nonlinear combination at 'adaptive'. CFP1 and CFP3 perform best when assessed by PCA; the most influencial components.

FIGURE 1

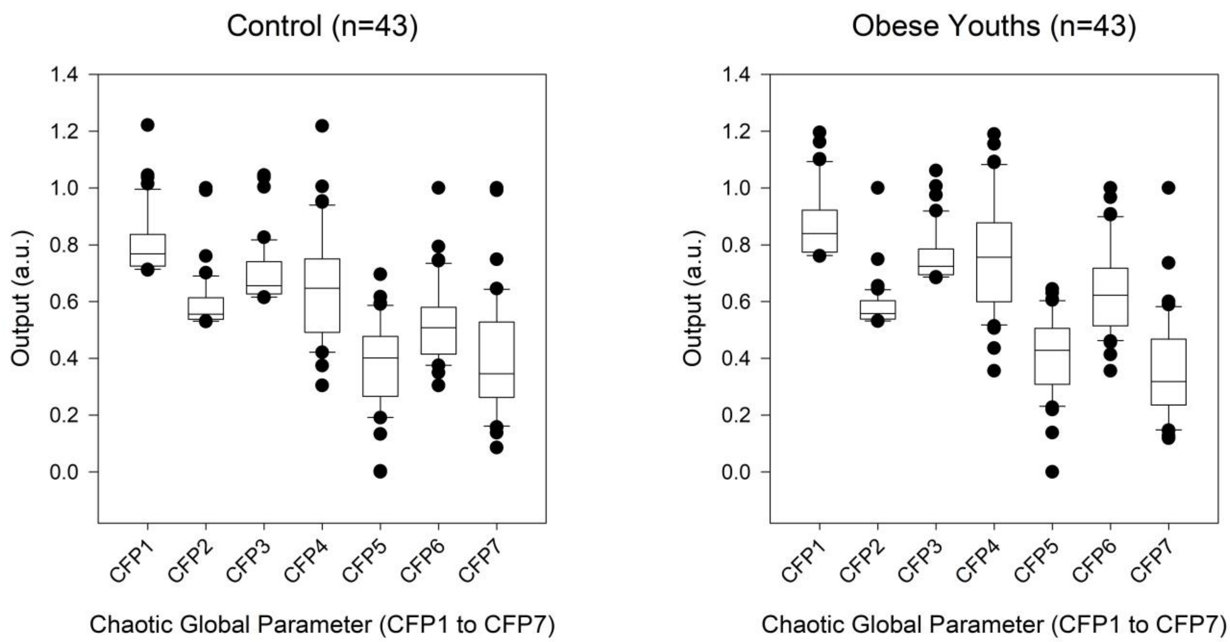
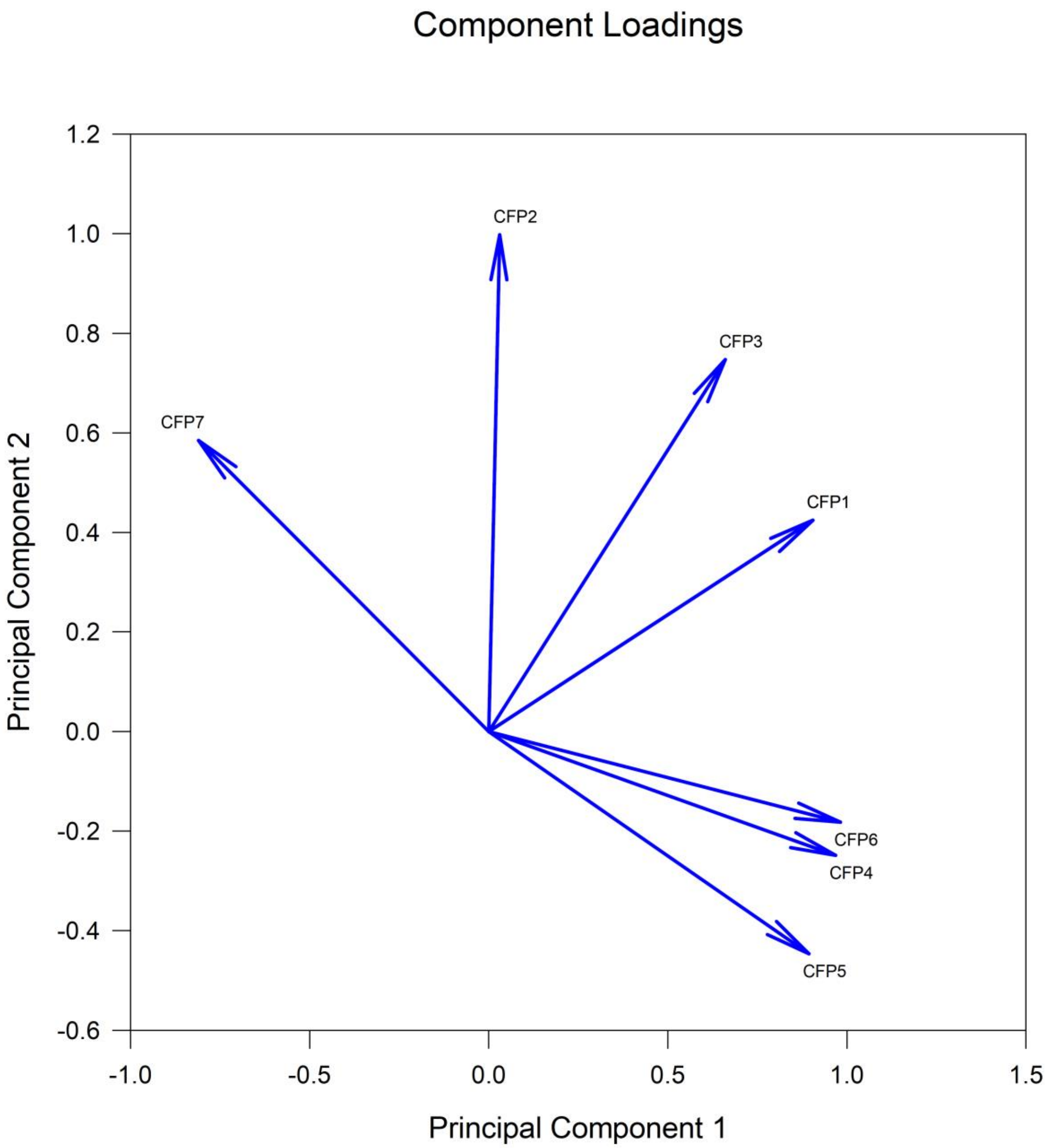

Control (n=43)
Obese Youths (n=43)
Output (a.u.)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
CFP1
CFP2
CFP3
CFP4
CFP5
CFP6
CFP7
Chaotic Global Parameter (CFP1 to CFP7)

FIGURE 2


Component Loadings
CFP2
CFP3
CFP7
CFP1
CFP6
CFP4
CFP5
Principal Component 2
Principal Component 1
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-1.0
-0.5
0.0
0.5
1.0
1.5