Recurrence Quantification Analysis of Sustained Sub-maximal Grip Force in Patients with Glycogen Storage Disease type III

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Abstract: Recurrence Quantification Analysis (RQA) was used to analyse sustained sub-maximal grip force of patients with Glycogen storage disease type III (GSD III) and control subjects. Recurrence plots (RP) of GSD III patients showed clear disruptions in comparison to control subjects. GSD III patients had more chaotic patterns that were less complex than those of control subjects. The RP of GSD III patients were less reliable than those of the controls, with changes between states occurring more often. The changes observed between the groups were not related to the fatigue induced by the experiment. The RQA technique is well suited for use with sustained grip-force signals.

Keywords: Nonlinear analysis, biomedical control, Chaos theory, signal processing

1. INTRODUCTION

Glycogen storage disease type III (GSD III) as an autonomic recessive metabolic disorder is characterized by a deficiency in glycogen disbranching enzymes (Zimakas and Rodd, 2005). Approximately 85% of patients with GSD III have both liver and skeletal muscles affected, with clinical examination revealing hepatomegaly. The progression of the disease results in conditions such as hypotonia and cardiomyopathy (Gremse et al., 1990). Abnormality in skeletal muscle mechanics of GSD III sufferers can be observed using grip force testing in conjunction with electromyography (Schwahn et al., 2002). The grip force testing has always been restricted to maximal force measures obtained from short-duration contractions. However, physiological time series, such as the grip force series, are by nature highly complex, exhibiting profoundly non-linear and non-stationary characteristics (Eke et al., 2002). The presence of such complexity is due to the interaction of multiple feedback loops to regulate each physiological process, as well as the involvement of many different structural units (Goldberger et al., 2002). In order to better analyse grip force, more advanced methods are required, to explain the complicated non-linear neuromuscular system. In this research, one such non-linear method was applied to grip force signals. The method chosen was recurrence quantification analysis (RQA). The first step of applying the RQA is the phase space reconstruction which converts the observed time series into a phase space. Based on the local recurrence or neighbourliness, of data points in the reconstructed phase space, a recurrence plot (RP) can be constructed. Because graphical representation may be difficult to evaluate, RQA was developed to provide quantification of important aspects revealed by the plot. The rationale behind the choice of RAQ as a tool in our research is based on the strongly non-linear, non-stationary nature of grip-force signals. Grip force is the output of a complex non-linear neuromuscular system for no adequate statistical model is available. Grip-force signals are non-stationary, and thus are not suited to traditional spectral analysis such as Fourier or Wavelet transforms, which can not provide enough information about the dynamic information contained in the signals. The RQA method has been shown to have a number of advantages, with applications in biomedical signal processing in EEG, EMG, and ECG (Marino et al., 2003, Farina et al., 2002, Del Santo et al., 2007, Gonzalez et al., 2000). The RQA can be used for short and noisy signals (Zbilut et al., 2002, Webber and Zbilut, 1994), a characteristic that is necessary for grip-force signal analysis. Accordingly, the RQA seems to be a suitable method for grip-force analysis, and fulfils the requirements of non-stationary, noisy short-duration signals. The objective of this study was to apply RQA to sustain sub-maximal grip force signals obtained from patients with GSD III and control subjects, in order to identify differences in force control strategies between the two groups.

2. METHODS

2.1 Subjects

Fifteen GSD III patients (7 males and 8 females) and 15 control subjects (9 males and 6 females) participated in the study. The subjects were assessed as part of a medical consultation that included the grip test. Ethical approval for the trial was obtained from the regional ethics committee (Hogrel et al., 2001). All subjects were provided with detailed information related to the study before giving their informed consent prior to testing. Characteristics of each subject group are shown in Table I.
2.2 Experimental Protocol

Subjects were seated on a chair facing a computer screen, with their shoulders adducted and their testing arm close to their body, with 180° of elbow extension and a small wrist extension. Each subject was tested only for their dominant hand. Maximal grip strength (MGS) values were evaluated as the maximal value of three maximal voluntary contractions lasting about three seconds, with one minute rest between trials (Table 1). After the MGS trials, subjects were given a five-minute rest before performing a sustained sub-maximal voluntary contraction (SMVC). For the SMVC subjects were required to maintain an isometric contraction at 70% of their MGS for 30 s within an acceptable region displayed on the screen of 65-75% of MGS). In order to eliminate psychological and random effects at the beginning and the end of the test, the first and last five seconds of the SMVC were removed and the remaining 20 s used for all subsequent analyses. Subjects were given verbal encouragement for all efforts.

<table>
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<tr>
<th>Table 1. Subject Characteristics</th>
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<tr>
<td>Age (y)</td>
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<tr>
<td>Height (cm)</td>
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<tr>
<td>Weight (kg)</td>
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<td>Maximal grip strength (kg)</td>
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2.3 Data Collection

Grip force data was measured using an MIE Grip Analyser (MIE Medical Research Ltd, Leeds, United Kingdom) with a resolution 1N/0.1kg and an accuracy of >1% of full scale output (1000 N). No subjects reported any problems with the handle size chosen. Data were collected using a BNC connection to a digital acquisition at a sampling frequency of 100Hz. Data acquisition was performed using a customised software program developed under Labview (Version 7.2; National Instruments, Austin, TX, USA), which enabled data to be collected and viewed in real-time. The MIE dynamometer and the data collection system were calibrated before and after each recording period.

2.4 Recurrence Quantification Analysis

The collected signals according to the experimental protocol were short time series that limited the application of signal processing. Furthermore, because of the complex and nonlinear aspects of the underlying physiological process, any attempt to apply a traditional linear method, such as the Fourier transform, fails to extract the required relevant information about the patient status.

In this work, we resort to nonlinear signal processing techniques adapted to the complexity and the short time aspects of the analyzed signals. Specifically, the phase space reconstruction method is an efficient technique providing a simple nonlinear tool to convert a scalar time series to vector trajectory from which many relevant parameters can be easily derived. A scalar time series \((u_1, u_2, ..., u_N)\) is transformed to an m-dimensional vector trajectory \((\vec{x}_1, \vec{x}_2, ..., \vec{x}_N)\) in the following way:

\[
\vec{x}_i = (u_i, u_{i-\tau}, ..., u_{i-(m-1)\tau})^T,
\]

where \(\tau\) is a time delay and \(m\) is the embedding dimension. In this study, the time delay \(\tau\) was selected as the first minimum of the mutual information function (Fraser and Swinney, 1986), while the embedding dimension \(m\) was chosen using the false nearest neighbours method (Kantz and Schreiber, 1995).

Several nonlinear parameters can be extracted from the phase-space trajectory. One particular aspect exploited in this study is the recurrence of the phase-space trajectory. This recurrence, introduced by Eckmann et al (Eckmann et al., 1987) can be expressed by the following matrix:

\[
R_{ij}^{\tau,\varepsilon} = \Theta(\varepsilon, -\|\vec{x}_i - \vec{x}_j\|),
\]

Where \(\varepsilon\) is a predefined threshold, \(\vec{x}\) is the trajectory point at time \(i\), \(\Theta(\chi)\) is the Heaviside function (i.e. \(\Theta(\chi) = 0\) if \(\chi < 0\), and \(\Theta(\chi) = 1\) otherwise) and \(\|\|\) is the Euclidean norm. The recurrence matrix (1) gives a graphical tool by plotting a dot where it is equal to 1. The obtained graph is referred to as the recurrence plot (RP). From the RP, some characteristic typologies like homogeneity, periodicity, presence of drifts or disrupted patterns of the dynamic system can be visually inspected (Marwan et al., 2007). An example of typical RP for a patient with GSD III and a control subject are shown in Fig 1.

However, because graphical representation may be difficult to evaluate in the RP, recurrence quantification analysis (RQA) was developed to provide quantification of important aspects revealed by the plot. This quantification of recurrence leads to several variables listed below:

\(a\)- The most common parameter is the recurrence rate (RR) or its percentage (%RR) which is a measure of the density of recurrence points in the RP:

\[
\%RR = \frac{1}{N^2} \sum_{i,j=1}^{N} R_{ij}^{\tau,\varepsilon} \times 100\%
\]

The %RR can be interpreted as the probability that a state returns to its \(\varepsilon\)-neighbourhood in the reconstructed phase space.

\(b\)- The percentage of the determinism (%DET) is the percentage of recurrence points which compose almost diagonal lines in the recurrence plot. The diagonal characteristics of RP reflects the repetitive occurrence of similar sequences of states in the observed system (Marwan et al., 2007). The %DET is computed as follows:
Each of the above variables provides relevant parameters about different nonlinear characteristics of the Grip force times series (Javorka et al., 2009). The reminder of the paper will be devoted to statistical analysis of these parameters and their relevance for discriminant analysis between patient and control groups.

2.5 Statistical Analysis

All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA). Results of RQA were calculated using the Cross Recurrence Plot toolbox 5.14(R27.1) of Matlab (The Mathworks, Natick, MA, USA; version 7.0.1). Measures of skewness and kurtosis, as well as the Kolmogorov-Smirnov test were used to check for normality (Fontes et al., 2001). A one-way ANOVA was used to test for differences between patients and control groups. A repeated measures ANOVA was used to study the effect of fatigue. Grip-force signals were divided into non-overlapping 5-s windows, with the RQA method applied to each window. Data were expressed as means and 95% confidence intervals. Alpha levels were set at \( p < 0.05 \).

3. RESULTS

Prior to applying RQA, the time delay \( \tau \), the embedding dimension \( m \) and the threshold \( \epsilon \) must be fixed. By using the mutual information criteria, the time delay \( \tau \) is fixed to 3 and by using the false nearest neighbours method, the embedding dimension \( m \) is fixed to 3. The threshold, \( \epsilon \), needs to be chosen such that the recurrence rate for the group of subjects with the least recurrence approaches 10% (Thiel et al., 2002). Such a recurrence rate can be obtained when \( \epsilon \) is equivalent to 10% of the mean phase space diameter (Thiel et al., 2002). Applying this principle, the threshold \( \epsilon \) is set to 0.01 for all grip force signals for both patients and controls.

Figures of sub-maximal grip force and corresponding recurrence plots (RP) from a patient with GSD III and a control subject are shown in Fig.1. These figures can be interpreted both qualitatively, as well as quantitatively. In the grip force figure, the only observable differences are that the GSD III patient has a decreasing force output over the course of the contraction, especially in the last 10 s. However, in the corresponding RP, clear differences can be observed. The RP of the patient has evidence of "disruptions", which means that some of the states are rare or differ greatly from a normal RP, with many transitions present in the data (Marwan et al., 2007). In addition, the RP of the patient has a fading towards the upper left and lower right corners, indicative of a trend and a drift. In contrast, the RP of the control subject has a quasi-periodic pattern, which is indicative of a regular cyclic process. The white lines that can be observed in the control RP around 6 and 18 s indicate the presence of transitions at these two times. It can also be observed that the period of the oscillations decreases in the control subject for the last two seconds. The disrupted trends of Fig. 1c were clearly visible in the RP figures for 12 of 15 patients, while the quasi-periodic pattern of Fig. 1d was observed in 13 of 15 control subjects.
Quantitative analysis of the RP was performed with the six variables identified in section 2.4. All variables were normally distributed, with the exception on Lmax, for which a log transform was performed. Significant differences were observed between control subjects and patients for all six parameters (Fig. 2; p<0.05). Lower values were found for GSD III patients than for the control subjects for all of these parameters.

The effect of fatigue was assessed using repeated measures ANOVA. The results of the fatigue analysis are shown in Fig. 3. There was a significant reduction in %RR and force level in all subjects, irrespective of the group (p<0.05). However, no significant differences were found for the other RQA parameters.

4. DISCUSSION

Recurrence Quantification Analysis is an advanced nonlinear method that has been successfully used in biomedical signal processing in a wide range of applications such as EEG, EMG, and ECG. The advantage of RQA is that it can be applied without prior assumptions on data size, stationarity or statistical distribution (Filibogi and Felici, 1999). The results of the present study demonstrate that RQA can also be used to analyse sustained grip-force signals. Significant differences were observed in all RQA parameters between the control and GSD III subjects. The %RR parameter quantifies the percentage of points that, over time, return to the same local neighbourhood in the reconstructed phase space. The %RR for patients was around 10%, as was expected given the method used to set the threshold (Thiel et al., 2002). In contrast, the control subjects had a three-fold increase in recurrence rate, indicating that control subjects grip-force signals often visit the same phase-space regions.

The %DET, Lmax and ENT parameters are based on the diagonal lines observed in the RP. A decrease in %DET is indicative of the reliability of the system, and the amount of repeatability present (Riley et al., 1999). The results of the present study demonstrate that GSD III patients have less reliable RP than do control subjects. Of particular interest is the Lmax parameter, which is inversely proportional to the largest Lyapunov exponent, which describes how fast trajectories diverge in the reconstructed phase space. The
decrease in Lmax in GSD III patients is indicative of a more chaotic, and therefore less stable, grip-force signal than that of the control subjects (Zbilut et al., 2002). The ENT parameter reflects the complexity of the signal of the deterministic structure of the time series (Bennett, 1990). The decrease in complexity of the deterministic component of GSD III patients is not in disagreement with the finding that GSD III patients had more chaotic grip-force signals. In fact, the signals observed in the present study, as for all biomedical signals, are a mixture of multiple types of systems, including both chaotic and deterministic. The decrease in complexity of the GSD III patients is in keeping with previous studies that have reported decreased complexity with a range of diseases such as Parkinson’s Disease, epilepsy, and manic depression (Lipsitz, 2004).

The TT parameter is an estimation of mean time that the system will remain at a specific state (Marwan et al., 2007), while Vmax can be used to find chaos-chaos transitions (Marwan et al., 2002). The GSD III patients had lower values of both TT and Vmax than the controls, indicating that subjects passed from one state to another, indicating a lower persistence than control subjects (Javorka et al., 2009). Similar findings have also been reported for ECG results (Tang et al., 2005).

In respect to changes due to fatigue, no significant trends were observed in the RQA variables for recurrence rate, diagonal lines, or vertical lines. This result is in contrast to that of EMG signals during fatigue, for which %DET decreased (Liu et al., 2004). However, other authors have found evidence that interpretation of %DET and fatigue is highly complicated, and depends on the nature of the effort, as well as the population studied (Morana et al., 2009).

5. CONCLUSIONS

Recurrence quantification analysis provides a useful method to analyse sub-maximal grip-force signals. Patients with GSD III were found to have grip-force signals that were more chaotic, but with a less complex deterministic component. These differences are possibly related to the underlying changes in metabolism of the GSD III patients. It would be of interest to apply this method to the study of other neuromuscular disorders. It might also be of interest to apply a decomposition method, in order to isolate the chaotic and deterministic components of the grip-force signals before applying the RQA method.

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