Assessment of autonomic function in patients with rheumatoid arthritis using spectral analysis and approximate entropy method

Ahmed Kamal, PhD, SMIEEE

Rheumatoid arthritis (RA) may produce dysfunction in the autonomic nervous system. However, this relationship has not been fully studied and some studies have conflicting results.1,2 Several studies found more excess cardiovascular mortality, cardiac failure, and sudden death in RA patients than in controls.3-8 Recent attention has focused on the importance of the long term pattern in heart rate, namely, heart rate variability (HRV) to assess and quantify autonomic function using simple statistical measures and power spectral analysis.

The aim of this study was to investigate the auto power spectra of HRV signals at different breathing rates as well as producing the gain frequency response for both healthy subjects (controls) and patients with RA. Another aim of this study was to introduce other statistics to assess the autonomic function developed from nonlinear dynamics. One such statistic is approximate entropy (ApEn), which quantifies the regularity of patterns in data set.9 The ApEn has been applied to the HRV signal for both controls and patients with RA.

Methods. Patients. We studied 51 healthy subjects (46±8.7 years) and 52 patients with RA (49±9.6 years) at Johns Hopkins Hospital, Maryland, United States during 2004 and 2005. We measured breathing at different rates, and the HRV signal derived from ECG. The auto-power and cross power spectra between HRV signal and breathing signal at different breathing rates was calculated, and the frequency gain response for both groups was obtained. The ApEn, described as a measure of regularity of HRV, was calculated for both patients with RA and the healthy control subjects.

Results: Both frequency gain response and ApEn measure were reduced in patients with RA in comparison with the control group. The power spectra of patients with RA showed a reduced high frequency (HF) value and higher low frequency for control subjects. However, the ApEn measure was significantly reduced in longer RA duration patients.

Conclusion: These findings suggest that the spectral analysis of HRV signal using breathing at different frequencies may detect an unbalance of the autonomic system of patients with RA, especially with increasing the sympathetic activity (higher low frequency) and reducing the parasympathetic tone (reduced frequency gain response), which can lead to sudden death in patients with RA. The ApEn may be a marker of RA stage.

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From the MIT Department, College of Engineering, Tennessee Tech University, Cookeville, Tennessee, United States of America.

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Address correspondence and reprint request to: Dr. Ahmed Kamal, MIT Department, College of Engineering, Tennessee Tech University, PO Box 5003, Cookeville 38505, Tennessee, United States of America. Tel. +1 931 528 1804. E-mail: akamal@tntech.edu

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wrists and ankle (Lead II). All the measurements were recorded for the duration of the experiments using a laptop computer. After the subject settled comfortably, a base line of the physiological measurements, ECG, derived HRV, and breathing signal were measured for 5 minutes for both the healthy subjects and patients with RA at rest in the supine position to calculate the ApEn and heart rate for each group, as shown in Figure 1. The subject was then asked to breathe deeply at different rates for 2 minutes following the light sequence, green inhale and red exhale. The cycle length is varied using a frequency generator and the light indicator automatically divides the cycle length into 40% inhalation and 60% exhalation. A rest period is allowed between each breathing rate sequence. The following breathing rates were examined for each subject at 3, 4, 6, 10, 12, 14, 16, 18, 24, and 30 breath/min. Figure 1 shows the block diagram of the experiments.

**Measurement and analysis of physiological signals.**
The ECG for each patient was fed into an electronic device, which detects the QRS-wave and measures the time until the next QRS wave occurs. The time between each successive QRS is called the R-R interval. Alternately, the peak of QRS was identified for each beat using rate-detector algorithm after exclusion of artifacts and ectopics. Those periods in which beat identification was poor were excluded from the analysis. This R-R time is converted into voltage directly proportional to that time. The reconstructed voltage signals as shown in Figure 2 may now be placed as HRV signals and can be interfaced to the laptop computer to obtain auto power and cross power spectra of HRV signal, and breathing signals at different rates using Fast Fourier transform (FFT) to calculate the gain frequency response and ApEn (Appendix 1*). The processing and analysis of HRV signals in this study were carried out at Tennessee Technological University, Cookeville, TN, USA.

**Identification procedure of frequency gain response.**
Consider a linear system with an input-output relationship as shown in Figure 3. It can be represented by a transfer function that can be found by several conventional methods, for example, impulse response, H(jw).R(jw), where H(jw) and R(jw) are the Fourier transform (using FFT algorithm) of the output signal h(t) and input signal r(t). If we define the transfer function between H(jw) and R(jw) as shown in Figure 3 as Grh = H/R, and multiply the numerator and denominator of the right side by R*(jw), namely, the complex conjugate of the Fourier transformed input r(t), the result is Grh(jw) = HR*/RR* = Prh*(jw)/Prr(w). Where Prh(jw) is the complex conjugate of the cross power spectrum between r(t) and h(t), and Prr(w) is the

*Appendix found at the end of the article.
auto-power spectrum of \( r(t) \). Assuming that \( n(t) \) and \( r(t) \) are not auto-correlated then \( Prh^*(jw) \) is not influenced by the presence of \( n(t) \). Since \( Prr(w) \) does not involve \( n(t) \) at all, this estimate of \( Grh(jw) \) (\( g(t) \) in time domain as shown in Figure 3), from \( h(t) \) and \( r(t) \) becomes a good method of overcoming the presence of noise to estimate \( H/R \) or the frequency gain response.

**Results.** Table 1 summarizes the clinical data of 52 patients with RA. There were no significant differences between RA and control in these parameters. However, the results of the HRV analysis and ApEn are shown in Figure 4 and Tables 2 & 3. Figure 4 shows the gain frequency response for both the RA group and the control group at different breathing rates. The gain frequency response of the control group is significantly higher (\( p=0.003 \)) than the RA group. Table 2 shows a significant difference (\( p=0.001 \)) between the value of ApEn of the HRV signal at rest for both groups. Table 3 shows the duration of RA in the patient group and ApEn as well as HRV parameters (heart rate, SDNN [standard deviation of all R-R intervals]) at rest.

**Discussion.** In this study, we introduced the new index ApEn to quantify the regularity of HRV. Lower ApEn indicates greater regularity and less variation of HRV signals and higher ApEn indicates greater regularity and more variation of HRV. Appendix 1 explains the approximate entropy method. Referring to Table 2, there is a significant reduction in both ApEn and SDNN in the RA group. Also, Table 3 shows a significant decrease in the ApEn index of RA patients related to the duration of the disease. However, SDNN and heart rate did not show a significant decrease with the duration of RA. This is an important finding to quantify the autonomic function of RA patients with respect to their duration of RA disease using ApEn index. In fact, a low ApEn correlates with greater system isolation, namely, less interaction between multiple inputs that makeup a normal control system.\(^{10,11}\) Several normal physiologic processes have been studied to demonstrate the relationship between ApEn and the integrity of the biological system. Kaplan et al.\(^{12}\) compared healthy young and elderly subjects and found reduced complexity in the elderly. Similarly, Rayan et al.\(^{13}\) demonstrated ApEn decreased with aging. In this study, we observed the lowest normalized ApEn values in RA patients with autonomic dysfunction. Also, we found a correlation between decreasing ApEn values and RA disease duration as shown in Table 3. The significance of the ApEn index is to represent one value (between 0 and 1), which indicates the quality of connection, interaction, regularity, and complexity in the system.

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**Table 1 - Clinical characteristics of patients (n = 52).**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>49 ± 1.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.7 ± 5.6</td>
</tr>
<tr>
<td>Mean disease duration (years)</td>
<td>8.4</td>
</tr>
<tr>
<td>ESR (mean ± SD)</td>
<td>42.6 ± 25.1</td>
</tr>
<tr>
<td>CRP (mean ± SD)</td>
<td>51.4 ± 124.6</td>
</tr>
</tbody>
</table>

BMI - body mass index, ESR - erythrocyte sedimentation rate, CRP - C-reactive protein

**Table 2 - Approximate entropy index (ApEn) and heart rate variability (HRV) signal (HRV) parameters (heart rate and standard deviation of all R-R intervals [SDNN]) at rest in patients with rheumatoid arthritis (RA) and controls.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RA group n=52</th>
<th>Control group n=51</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApEn</td>
<td>0.76 ± 0.15</td>
<td>0.98 ± 0.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Heart rate (beats/sec)</td>
<td>75.6</td>
<td>70.4</td>
<td>0.15</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>98.6 ± 36.8</td>
<td>152.3 ± 18.4</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**Table 3 - Heart rate variability (HRV) parameters (heart rate and standard deviation of all R-R intervals [SDNN]) and approximate entropy index (ApEn) at rest in patients with rheumatoid arthritis (RA) according to duration of disease.**

<table>
<thead>
<tr>
<th>Duration of RA</th>
<th>1-3 years n=17</th>
<th>3-6 years n=20</th>
<th>&gt;6 years n=15</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApEn</td>
<td>0.88 ± 0.09</td>
<td>0.73 ± 0.1</td>
<td>0.64 ± 0.14</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart rate (beats/sec)</td>
<td>72 ± 2.6</td>
<td>76 ± 3.2</td>
<td>79 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>101 ± 8.6</td>
<td>95 ± 10.3</td>
<td>90 ± 6.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS - not significant
Applying this concept to the autonomic nervous system of RA patients, it seems their autonomic system lacks the integrity and interaction with respect to normal healthy subjects, which may be manifested in low ApEn values in the RA group as shown in Table 3. The frequency gain response as shown in Figure 4 demonstrates the influence of breathing on gain response with respect to RA patients and healthy subjects. The healthy subject group exhibits 2 distinct peaks at nearly 6 cycles/min (0.1 Hz) and nearly 15 cycles/min (2.5 Hz). However, the RA group shows only one lower distinct peak at the same breathing rate 6 cycles/min. Clearly, RA patients show lower gain response to breathing than the healthy subjects at all breathing frequencies. This may be attributed to a decrease in autonomic function, specially parasympathetic activities in RA patients. These observations are important with respect to the increased rate of sudden death occurring in RA patients, which correlated the sudden death with decreased vagus (parasympathetic) activity. Our findings, which correlate the duration of RA disease and ApEn may be considered a simple prognostic value to assess the autonomic function of patients with RA.

References

Appendix 1 - Approximate entropy.

Approximate entropy (ApEn) was calculated for 500 consecutive intervals of ECG,44 Given an input of N data points u(1),u(2),…,u(N), 2 input parameters, m and r, must be fixed to compute ApEn [denoted precisely by ApEn (m,r,N)]. To define ApEn, first-form vector sequences x(1) through x[N-(m+1)] from the u[u(I)], defined by x(i)={u(i),….,u[i+(m-1)]}. These vectors represent m consecutive u values, commencing with ith point. Briefly, ApEn measures the logarithmic likelihood that runs of patterns that are close (within r) for m contiguous observations remain close (within the same tolerance width r) on next incremental comparisons. Lower ApEn indicates greater regularity and higher ApEn indicates greater complexity. For the purpose of the current study, m=2, N=500, and r =10 for our calculation. For many models, ApEn and standard deviation can be correlated. In order to determine the independent influence of complex and variability, normalized ApEn was calculated using r=20% of the standard deviation of the same heart rate series.