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

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ABSTRACT

Objectives: To assess the effect of rheumatoid arthritis (RA) on autonomic function of a group of RA patients in comparison with a normal control group by measuring the frequency gain response of the 2 groups. Also, to determine whether the duration of RA correlated with measures of heart rate variability signal (HRV) using an approximate entropy index (ApEn).

Methods: We evaluated 52 patients with RA, and 51 matched healthy subjects at the Arthritis Center, 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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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, USA during 2004 and 2005. None of the RA patients had clinical signs of myocardial infraction, arterial hypertension, diabetes mellitus, including type I and II, or pulmonary disease. No drugs that could affect HRV parameters were used by the subjects and the control groups under study. Four RA patients who were smoking at least one cigarette per day were excluded from this study. Therefore, the final group consisted of 52 RA patients. All participants gave their informed consent and the Institutional Review Board approved the study protocol. With each subject lying supine, the breathing signal was measured using a thermistor placed in the nose. An ECG was taken from

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.[10] 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.

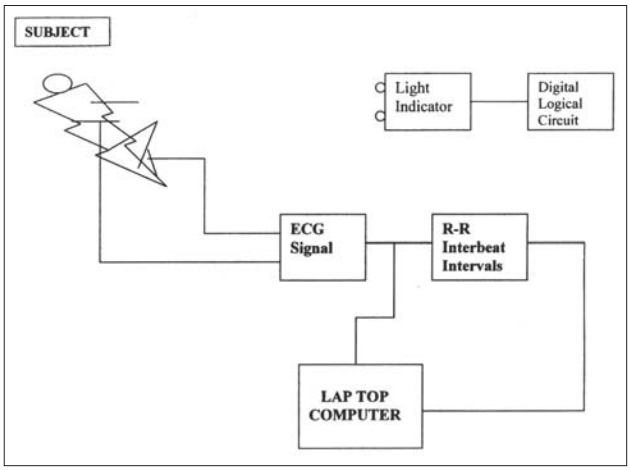

Figure 1 - Block diagram of experimental procedure.

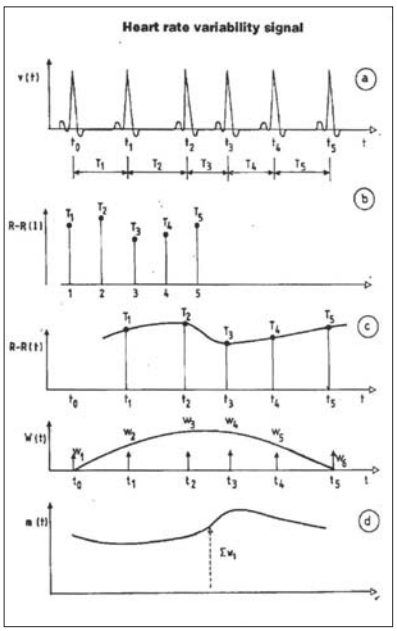

Figure 2 - Derivation of heart rate variability (HRV) signal from ECG showing **a**) ECG, **b**) detection of R-R interval, **c**) construction of heart rate variability (HRH) signal, and **d**) smoothed HRV signal.

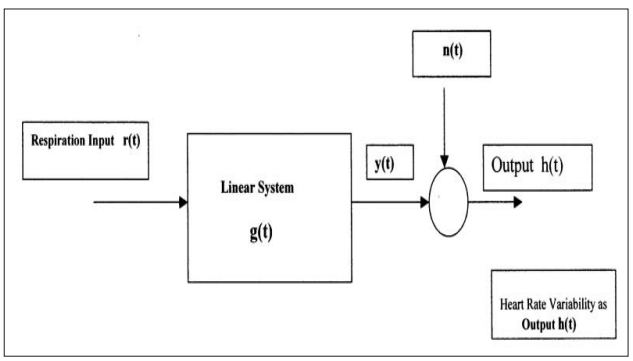

Figure 3 - Relationship between input (breathing) and output (heart rate variability signal).

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

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

Variable	Value
Age (years), mean ± SD	49 ± 1.6
BMI (kg/m^2)	25.7 ± 5.6
Mean disease duration (years)	8.4
ESR (mean ± SD)	42.6 ± 25.1
CRP (mean ± SD)	51.4 ± 124.6

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

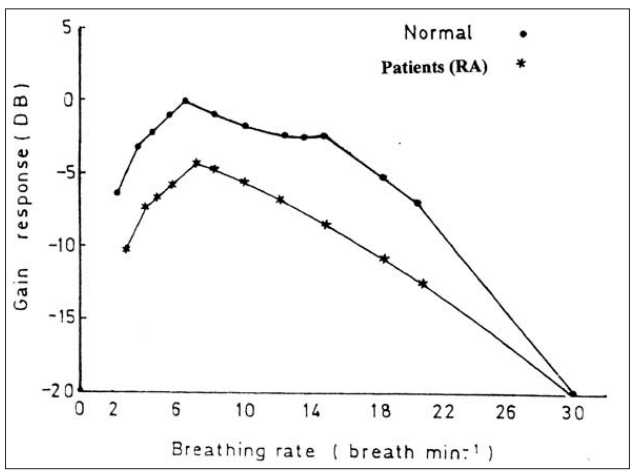

Figure 4 - The average frequency gain response of healthy subjects and patients at different breathing rates.

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

Parameter	RA group n=52	Control group n=51	*P*-value
ApEn	0.76 ± 0.15	0.98 ± 0.1	<0.05
Heart rate (beats/sec)	75.6	70.4	0.15
SDNN (ms)	98.6 ± 36.8	152.3 ± 18.4	0.003

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.

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

NS - not significant

(**Appendix 1**). 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 subjects 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.[7] 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

1. Louthrenoo W, Ruttanaumpawan P, Aramrattana A, Sukitawut W. Cardiovascular autonomic nervous system dysfunction with rheumatoid arthritis and systemic lupus erythematosus. ***QJM*** 1999; 92: 97-102.
2. Maule S, Quadri R, Marinate D, Pellerito RA, Marucco E, Marinone C, et al. Autonomic nervous dysfunction in systemic lupus erythematosus and rheumatoid arthritis: possible pathogenic role of autoantibodies to autonomic nervous structures. ***Clin Exp Immunol*** 1997; 110: 423-427.
3. Kvalvik AG, Jones MA, Symmons DPM. Mortality in a cohort of Norwegian. patients with rheumatoid arthritis followed from 1977 to 1992. ***Scand J Rheumatol*** 2000; 29: 29-37.
4. Monson RR, Hall PP. Mortality among arthritics. ***J Chronic Dis*** 1976; 29: 459-467.
5. Mutru O, Laakso M, Isomaki H, Koota K. Ten years mortality and causes of death in patients with rheumatoid arthritis. ***BMJ*** 1985; 290: 1797-1799.
6. Prior P, Symmons DPM, Scott DL, Brown R, Hawkins CF. Cause of death in rheumatoid arthritis. ***Br J Rheumatol*** 1984; 23: 92-99.
7. del Rincon I, Williams K, Stern MP, Freeman GL, Escalate A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. ***Arthritis Rheum*** 2001; 44: 2737-2745.
8. Riise T, Jacopsen BK, Gran JT, Haga HJ, Arnesen E. Total mortality is increased in rheumatoid arthritis. A 17 year prospective study. ***Clin Rheumatol*** 2001; 20: 123-127.
9. Pincus SM. Approximate entropy as a measure of system complexity. ***Proc Natl Acad Sci USA*** 1991; 88: 2297-2301.
10. Pincus SM. Greater signal regularity may indicate increased system isolation. ***Math Biosci*** 1994; 122: 161-181.
11. Pincus SM, Goldberg AL. Physiological time series analysis: What does regularity quantify? ***Am J Physiol*** 1994; 266: 1643-1656.
12. Kaplan DT, Furman MI, Pincus SM, Rayan SM, Lipsitz LA, Goldberger AL. Aging and the complexity of cardiovascular dynamics. ***Biophys J*** 1991; 59: 945-949.
13. Rayan SM, Goldberg AL, Pincus SM, Mietus J, Lipsitz LA. Gender and age related differences in heart rate dynamics: are women more complex than men? ***J Am Coll Cardiol*** 1994; 24: 1700-1707.
14. Pincus SM, Gladstone IM, Ehrenkranz MS. A regularity statistics for medical data analysis. ***J Clin Monit*** 1991; 7: 335-345.

Appendix 1 - Approximate entropy.

Approximate entropy (ApEn) was calculated for 500 consecutive intervals of ECG.[14] 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.