

Influence of Atropine on Fractal and Complexity Measures of Heart Rate Variability

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Background: Measurement of short-term fractal-like correlation properties of heart rate dynamics has been shown to be a useful prognostic indicator of adverse events in cardiac patients. Complexity measurements of heart rate variability (HRV) have already provided important information in many cardiac conditions. However, data on the physiological background of these newer nonlinear measures of HRV are limited.

Methods: Nine healthy subjects (aged from 22 to 35 years, 6 males, 3 females) had an electrocardiographic (ECG) recording during controlled breathing in supine position. HRV was analyzed for 5 min periods before and after intravenous injection of 0.6 mg of atropine using conventional HRV measures and newer nonlinear HRV measures including the short-term scaling exponent (α_1) and approximate entropy (ApEn).

Results: The short-term scaling exponent α_1 increased significantly after atropine injection (1.01 ± 0.23 vs 1.43 ± 0.19 , $P = 0.001$). There was no significant difference between ApEn values before and after atropine injection (0.87 ± 0.17 vs 0.70 ± 0.31 , respectively, $P = 0.27$). At baseline before atropine administration, α_1 had a significant negative correlation with SDNN, RMSSD, and HF ($r = -0.70, -0.76, -0.67$, respectively, $P < 0.05$ for all), and a significant positive correlation with heart rate ($r = 0.76$, $P < 0.05$). After atropine injection, α_1 did not have significant correlation with any of the HRV parameters or heart rate. There were no significant correlations between ApEn and any of the HRV measures or heart rate either before or after atropine administration.

Conclusions: Vagal tone has an important influence on the values of the short-term scaling exponent α_1 . However, vagal modulation is not a major determinant of the values of ApEn.

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Newer fractal and complexity measures of heart rate variability (HRV) may reveal more subtle changes in control systems of sinus node firing than traditional HRV parameters. The short-term scaling exponent (α_1), which provides an estimation of fractal-like correlation properties of heart rate dynamics, has been shown to be a useful predictor of adverse cardiac events in several studies.¹⁻³ Approximate entropy (ApEn), a measure of complexity of heart rate time series, has already

provided valuable information in various cardiac conditions.⁴⁻⁸ Despite these advancements in HRV analyses, little is known about the regulatory systems of fractal and complexity properties of heart rate dynamics. Our study aimed to assess the influence of parasympathetic blocking on fractal-like correlations and complexity of heart rate behavior by comparing the values of α_1 and ApEn before and after injection of atropine in healthy subjects during controlled conditions.

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METHODS

Study Subjects

The study population consisted of 9 healthy subjects (aged from 22 to 35 years, 6 males and 3 females). The subjects were examined by a cardiologist. The study subjects did not have any history or symptoms of chronic diseases, any continuous medications, abnormal clinical findings, or contraindications for the study. All these healthy volunteers signed a consent form approved by the Human Investigation Committee of the Strong Memorial Hospital, Rochester, New York.

Study Protocol

Electrocardiographic (ECG) recorders (Diagnostic Medical Instruments, Syracuse, NY, USA) were applied to study subjects and intravenous line inserted. The subjects breathed room air at 10 cycles/min for 5 minutes during which an ECG recording was obtained. Respiratory rate was controlled with the use of a metronome. Afterwards the study subjects breathed room air for 10 minutes, and atropine 0.6 mg was administered intravenously. The subjects breathed room air at the control rate of 10 cycles/minute for another 10 minutes during which an ECG recording was obtained. The experiments were conducted in the morning, and the subjects were kept in a supine position for the whole duration of the experiment.

Analysis of Heart Rate Variability

HRV was analyzed for a 5-minute period before atropine administration from the data obtained at the first step of the study protocol while the subjects were breathing room air at 10 cycles/min for 5 minutes. HRV also was analyzed for 5 minutes after atropine administration while the subjects were breathing room air at 10 cycles/min. Premature depolarizations were deleted from the ECG data. HRV was analyzed by a software package with methodology previously described in detail.^{5,9-11} Traditional statistical and newer nonlinear parameters of HRV were determined.

The standard deviation of all normal-to-normal R-R intervals (SDNN), the square root of the mean squared differences of successive normal-to-normal R-R intervals (RMSSD), the low frequency power of power spectrum (LF, 0.04–0.15 Hz) and the high frequency power of power spectrum (HF,

0.15–0.40 Hz), and LF/HF ratio were calculated as standard conventional measures of HRV. The fast Fourier transformation method was used to obtain the spectral components of power spectrum. LF and HF were expressed in absolute and normalized units (nu). The normalized units were obtained by dividing each component of power spectrum by total variance and multiplying the value by 100.

The short-term scaling exponent (α_1) and approximate entropy (ApEn) were determined as nonlinear parameters of HRV. The α_1 describes short-term fractal-like correlation properties^{12,13} and ApEn complexity^{5,14} of the R-R interval time series. The parameter α_1 describes the self-similarity properties of time series. For totally uncorrelated data it has a value of 0.5 (corresponding to white noise) and has higher values when the time series shows correlation properties (fractal organization), a value = 1 indicates 1/f signal properties, and a value = 1.5 indicates Brownian noise (smoother fluctuations). ApEn quantifies the likelihood that runs of patterns that are close remain close on next incremental comparisons and the larger the value of approximate entropy, the greater the unpredictability in the data time series. The complexity of relatively small data sets can also be assessed using ApEn. The ApEn input variable m determines the window length of compared runs of R-R interval data, and the variable r sets the tolerance for the comparison of these runs. The input variables m and r must be fixed to calculate approximate entropy, and $m = 2$ and $r = 20\%$ of the SD of the data sets were chosen as suitable values based on the previous findings of statistical validity.¹⁴

Statistical Analysis

Paired *t*-test was used to assess statistical significances of differences of HRV parameters obtained before and after administration of atropine. Pearson's correlation coefficients were determined to study the correlations between different HRV parameters. A P value < 0.05 was considered statistically significant.

RESULTS

The values of the short-term scaling exponent α_1 were significantly higher after atropine administration compared with the values obtained before at-

Table 1. Heart Rate Variability Parameters and Heart Rate in Study Subjects at Baseline and After Atropine Administration

	Baseline	After Atropine	P Value
Heart Rate (beats/min)	78 ± 13	86 ± 17	0.06
<i>Nonlinear HRV Parameters</i>			
α_1	1.01 ± 0.23	1.43 ± 0.19	0.001
ApEn	0.87 ± 0.17	0.70 ± 0.31	0.27
<i>Traditional HRV Parameters</i>			
SDNN, ms	48 ± 25	58 ± 36	0.47
RMSSD, ms	39 ± 29	18 ± 21	0.003
LF power ms ²	316 ± 252	673 ± 1322	0.35
nu	15 ± 7	20 ± 11	0.36
HF power ms ²	2040 ± 3113	265 ± 635	0.07
nu	58 ± 21	7 ± 5	< 0.001
LF/HF Ratio	0.34 ± 0.25	4.15 ± 3.26	0.008

The values are means ± SD. HRV = heart rate variability; α_1 = the short-term scaling exponent; ApEn = approximate entropy; SDNN = the standard deviation of all normal-to-normal R-R intervals; RMSSD = the square root of the mean squared differences of successive normal-to-normal R-R intervals; LF = the low frequency power of power spectrum; nu = normalized units; HF = the high frequency power of power spectrum.

ropine injection (Table 1, Fig. 1). However, atropine administration did not cause significant changes in ApEn values (Table 1, Fig. 1).

The RMSSD values were significantly lower after atropine injection compared with the values obtained before atropine administration (Table 1, Fig. 1). Atropine administration did not change the SDNN values significantly (Table 1, Fig. 1). HF in absolute units tended to decrease and HF in nu decreased significantly after atropine injection (Table 1). There were no significant differences between the LF values obtained before and after atropine administration (Table 1). The LF/HF ratio values were significantly higher after atropine injection compared with the values obtained before atropine administration (Table 1). Heart rate tended to increase after atropine injection (Table 1).

The short-term scaling exponent α_1 had a significant negative correlation with SDNN, RMSSD, and HF, and a significant positive correlation with heart rate at baseline before atropine administration (Table 2). After atropine administration, α_1 did not show significant correlation with any of the HRV measures or heart rate (Table 2). There were no significant correlations between ApEn and the HRV measures or heart rate either before or after atropine injection (Table 2).

DISCUSSION

The results of the present study show that parasympathetic blocking by atropine increases signif-

icantly the short-term scaling exponent α_1 in healthy subjects during controlled conditions. There were no significant changes in ApEn in these settings.

Previous data on the physiological background of fractal-like correlation properties of heart rate dynamics are limited. It has been hypothesized that autonomic and respiratory influences¹² and neurohumoral activation, e.g., sympathoexcitation,^{2,15} may alter short-term correlation properties of heart rate behavior. Tulppo et al. showed that the short-term scaling exponent α_1 increases during the passive head-up tilt test and exercise in healthy subjects.¹⁶ At the same time, they found a decrease in the normalized high-frequency spectral component and an increase in the low-frequency component of HRV. These observations suggest that reduced vagal and enhanced sympathetic outflow increase the values of α_1 . However, recent data about effects of pharmacological modulation on short-term correlation properties of heart rate dynamics in healthy men suggest that increased levels of circulating noradrenaline decrease α_1 values, which may also be a result from the concomitant noradrenaline-induced baroreceptor-mediated vagal activation.¹⁷ Furthermore, elevation of α_1 values was observed after pharmacological vagal blockade.¹⁷ Our present findings are in good alignment with these notions showing that atropine significantly increases the short-term scaling exponent α_1 . RMSSD and HF in nu decreased

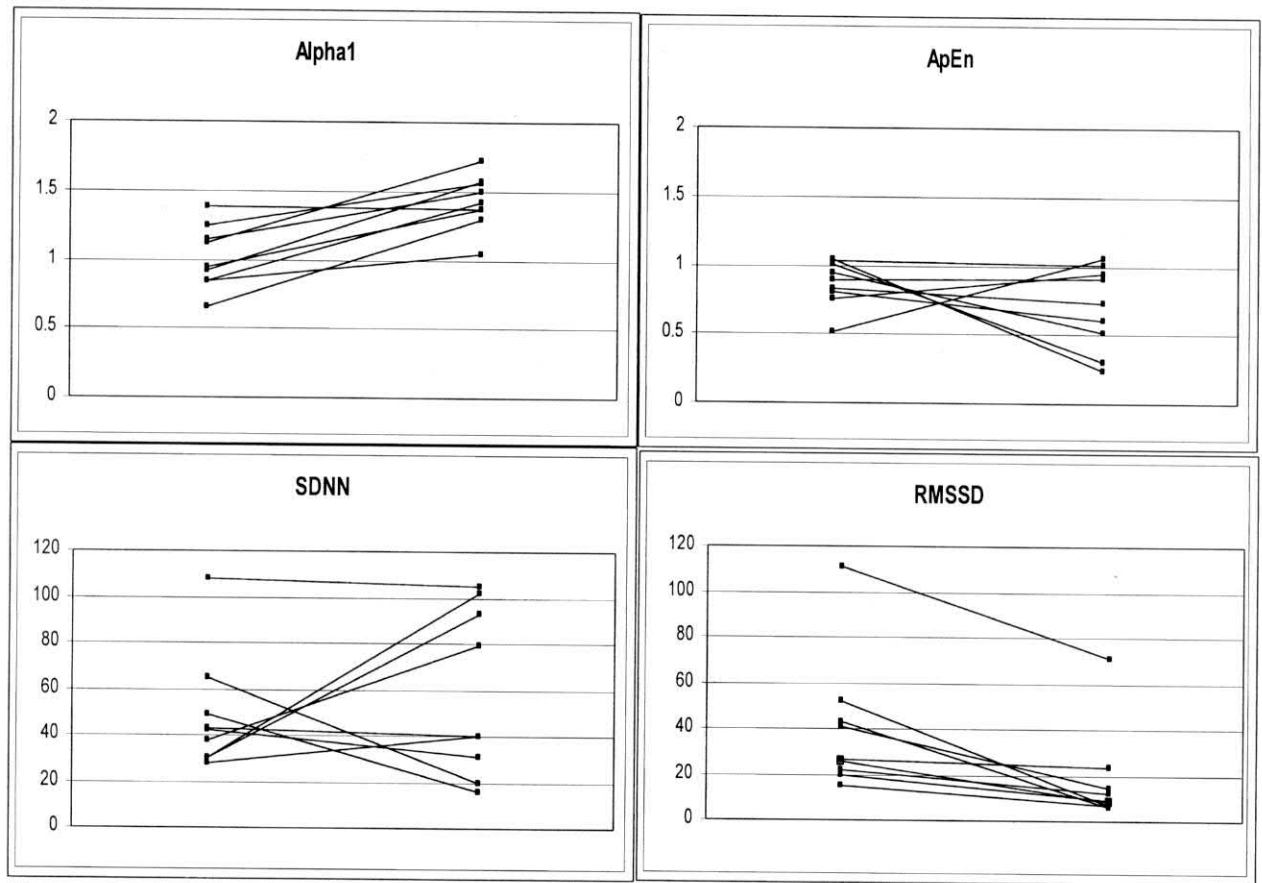


Figure 1. The α_1 (Alpha1), ApEn, SDNN, and RMSSD at baseline (left-sided values) and after atropine administration (right-sided values) in the study subjects. Abbreviations as in Table 1.

significantly in the present healthy population after atropine further confirming the involvement of vagolytic influences in increase of α_1 values. At baseline, the short-term scaling exponent α_1 had a significant negative association with RMSSD, HF, and SDNN, and a significant positive association with heart rate, an observation that can be explained by

relation of these parameters with vagal tone. This concept is further supported by the present finding that none of the HRV parameters showed significant association with α_1 after parasympathetic blocking by atropine.

In a few recent studies, the short-term scaling exponent α_1 has been shown to be better predictor

Table 2. Correlation of Heart Rate Variability Parameters at Baseline and After Atropine Administration

	α_1	ApEn	SDNN	RMSSD	LF	HF	LF/HF	HR
<i>Baseline</i>								
α_1		0.29	-0.70*	-0.76*	-0.51	-0.67*	0.49	0.76*
ApEn	0.29		-0.31	-0.34	-0.32	-0.28	0.28	0.08
<i>After Atropine</i>								
α_1		-0.61	0.27	-0.17	-0.06	-0.20	0.35	0.20
ApEn	-0.61		-0.56	0.26	0.23	0.28	-0.07	-0.20

The values are Pearson's correlation coefficients. HR = heart rate; the other abbreviations are the same as in Table 1. * = significant at the $P < 0.05$ level.

of adverse events than the conventional HRV measures in cardiac patients.¹⁻³ However, the mechanisms underlying the association between decreased α_1 values and adverse events are poorly understood. Although our present observations and previous data^{16,17} indirectly suggest that increased parasympathetic tone may decrease the values of the short-term scaling exponent α_1 in normal subjects, this concept cannot be directly extrapolated to cardiac patients with decreased left ventricular function as the HRV counterparts of autonomic drives are different in heart failure patients than in healthy subjects.¹⁸ Nevertheless, the abovementioned recent observation showing that noradrenaline (adrenergic modulation) decreases α_1 values in healthy men¹⁷ is in good alignment with the recent data that showed that beta-blocker therapy (antiadrenergic modulation) increases the short-term scaling exponent in patients with advanced congestive heart failure indicating the reversal of the deteriorated heart rate scaling behavior.¹⁹ These notions are interesting in light of the previous observations which show that high levels of plasma noradrenaline increase²⁰ and beta-blocker therapy decreases mortality in patients with heart failure.²¹

The data on the physiological counterparts of ApEn analyzed from heart rate fluctuations are not well established. Parasympathetic blockade has been shown to cause only minimal changes in ApEn in healthy men.²² Our present observations are in agreement with these previous findings showing no significant changes in ApEn after atropine administration in healthy subjects during controlled conditions. Thus, the present and previous²² data suggest that vagal tone is not a major determinant of ApEn. It has been reported that ApEn increases during exercise after the ventilatory threshold level and during exercise after atropine²² supporting the concept that sympathetic activation increases ApEn. We did not find any significant association between ApEn and LF or any other HRV parameter either at baseline or after atropine administration in the present healthy study population, suggesting that the low level of sympathetic activity during controlled resting conditions does not influence the values of ApEn. Furthermore, observations in patients with advanced congestive heart failure have shown that antiadrenergic therapy by a beta-blocker does not change the ApEn values.¹⁹ Alterations of the ApEn values have been attributed to various cardiac conditions.^{4-8,23}

However, the mechanisms of the regulatory systems of heart rate dynamics that cause these changes in ApEn remain to be resolved.

The limitations of the present study include a small sample size and a consequent limited statistical power. In addition, the length of the ECG recordings used for HRV analysis was relatively short. The atropine dose was somewhat small. That may have resulted only in partial parasympathetic blockade.

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