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Nonlinear analysis of heart rate dynamics in hyperthyroidism

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Abstract

Studies on the physiology of the cardiovascular system suggested that the generation of the heart rate signal is governed by nonlinear chaotic dynamics. No study investigated the nonlinear dynamics of heart rate in hyperthyroidism. We examined whether the heart rate dynamics of hyperthyroid patients is different from normal controls by the nonlinear analysis of heart rate variability (HRV) with correlation dimension (CD). Thirty-three hyperthyroid Graves' disease patients (30 females and 3 males; age 31 ± 1 years, means ± SE) and 33 sex-, age-, and body mass index-matched normal controls were recruited to receive one-channel electrocardiogram recording for 30 min. The CD, an index of complexity, was computed from the sequence of normal R–R intervals by the Grassberger and Procaccia algorithm. Compared to the normal controls, the hyperthyroid patients showed significant reductions ($P < 0.001$) in the mean R–R interval (hyperthyroid 616 ± 15 versus control 868 ± 16 ms), the standard deviation of R–R intervals (25 ± 2 versus 54 ± 4 ms) and CD (5.02 ± 0.11 versus 6.42 ± 0.16). Our study demonstrated for the first time that hyperthyroid patients and normal controls could be distinguished by CD analysis of HRV. In addition, the decreased CD in hyperthyroid patients implies reduced complexity and impaired tolerance to cardiovascular stresses in hyperthyroidism. This finding helps to explain exercise intolerance and irritability manifested by the hyperthyroid patients.

Keywords: nonlinear dynamics, heart rate variability, hyperthyroidism, correlation dimension, complexity, chaos

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1. Introduction

The observation that hyperthyroid patients manifest symptoms and signs similar to those of hyperadrenergic states implies autonomic dysfunctions in hyperthyroidism (Levey and Klein 1990). The analysis of heart rate variability (HRV) provides a non-invasive and sensitive tool for the evaluation of autonomic control of the heart (Akselrod *et al* 1981, Task Force 1996). In clinical applications, decreased HRV is associated with increased cardiac mortality after acute myocardial infarction (Kleiger *et al* 1987). In addition, reduced HRV is an early warning sign of diabetic neuropathy among diabetic patients (Ewing *et al* 1991, Malpas and Maling 1990).

In general, HRV analysis could be grouped into linear and nonlinear methods (Task Force 1996). The linear methods consist of the time domain and the frequency domain methods. The nonlinear methods are mainly derived from the chaos theory. Traditionally, the beat-to-beat variation exhibited by the sinoatrial node is analyzed with linear methods. In applying HRV analysis to investigate the autonomic nervous system of hyperthyroid patients, previous studies have mainly focused on the linear methods. The time domain analysis of HRV revealed a decrease in the mean R–R interval, the standard deviation of R–R intervals (SDNN), the root mean square of successive differences between adjacent R–R intervals (RMSSD), the percentage of differences between successive R–R intervals >50 ms (pNN50), etc in the hyperthyroid patients compared with the normal controls (Petretta *et al* 2001, Osman *et al* 2004). These results signify reduced vagal modulation of heart rate in hyperthyroidism. Previous studies of the frequency domain analysis of HRV mainly indicated that hyperthyroid patients showed a decrease in total power (TP), very low frequency power (VLF), low frequency power (LF), high frequency power (HF) and HF in normalized units (HF%) as well as an increase in LF in normalized units (LF%) and in the ratio of LF to HF (LF/HF) compared with the normal controls (Cacciatori *et al* 1996, Burggraaf *et al* 2001, Chen *et al* 2006). Such results suggest increased sympathetic and decreased vagal modulation of heart rate in hyperthyroidism.

However, the sinoatrial node is affected by multiple nonlinear mechanisms (sympathetic nerves, vagal nerves, hormones, hemodynamics, etc), most of which have long feedback loops compared with the basic sinus cycle length. In addition, the above affecting factors interact with each other. These constitute a possible substrate for the generation of chaos (Denton *et al* 1990, Goldberger 1996). As a result, the heart rate system is not constant on time, does not show regular periodicity and may not be completely described by a linear analysis. Thus, a nonlinear analysis of HRV appears to be more appropriate to interpret the complex phenomena of heart rate dynamics. In recent years, nonlinear analysis of physiological dynamics has been applied to the studies of heart rate (Babloyantz and Destexhe 1988, Elbert *et al* 1994, Goldberger *et al* 2002, Guevara *et al* 1981, Stein *et al* 1992), electroencephalographic activity (Mayer-Kress and Layne 1987, Elger and Lehnertz 1998), respiratory waveforms (Hoyer *et al* 1997), hormone secretion rhythmicity (Hartman *et al* 1994, Meneilly *et al* 1997, Veldman *et al* 2000), etc.

Chaos refers to an aperiodic, seemingly random behavior in a deterministic system. It is neither periodic nor completely random, but has characteristics of both. In the analysis of HRV, we regard the R–R interval time series as a system to be studied. If this time varying R–R interval series is a chaotic system, its trajectories in the state space would form a strange attractor (Mandelbrot 1982). We can evaluate the characteristics of a nonlinear system by studying the geometric features of its attractor. This geometry may provide important clues about the nature of the trajectory dynamics. The geometric features of an attractor could be quantified by its dimensionality. In fact, the dimensionality of an attractor gives us an estimate of the number of active degrees of freedom for the system. In addition, the

dimensionality is related to the number of dynamic variables required to reconstruct the state space of the system. Because a non-integer, i.e. a fraction rather than an integer, dimension will present when calculating the dimension of an attractor from a chaotic system, the term fractal dimension is used to describe the geometric features of an attractor. There are many different methods for computing the fractal dimension of an attractor. Correlation dimension (CD) has been widely used to characterize chaotic attractors (Grassberger and Procaccia 1983a, 1983b). In this study, we used CD to evaluate the fractal dimension of the R–R interval time series system.

The current gold standard of diagnosing hyperthyroidism is the measurements of serum thyroid hormone and thyrotropin concentrations. However, the analysis of HRV could help us in understanding not only the modulation of the cardiac autonomic nervous system but also the characteristics of the heart rate dynamics. Thus, it could further help us to differentiate and classify clinical pathologic populations (Akselrod *et al* 1981, Task Force 1996). To the best of our knowledge, there has not been a study on the nonlinear analysis of HRV in the hyperthyroid patients. We designed the current study to analyze the CD of R–R interval time series in the hyperthyroid patients as well as the normal control subjects and to investigate whether it is possible to distinguish hyperthyroid patients from normal control subjects by CD analysis of HRV.

2. Subjects and methods

2.1. Subjects

We studied 33 newly diagnosed, untreated hyperthyroid Graves' disease patients from the outpatient clinic of a university hospital and a group of 33 healthy normal control subjects. The hyperthyroid and control groups were matched for sex (30 females and 3 males versus 30 females and 3 males, hyperthyroid versus control), age (31 ± 1 versus 30 ± 1 years, means $\pm$ SE) and body mass index (20.6 ± 0.3 versus 21.5 ± 0.5 kg m^{-2}). The diagnosis of Graves' disease was established on the basis of clinical, biochemical, immunological, thyroid scintigraphic scanning and uptake data. Individuals with cardiac arrhythmia, cardiovascular disease, diabetes, pregnancy, or those using medication were excluded. The study protocol was approved by the local ethics committee, and informed consent was obtained from all participants. The study was conducted according to the principles of the Helsinki declaration.

2.2. Study protocol

The hyperthyroid patients were studied at the time of diagnosis, before any medication was administered. No alcohol or caffeine-containing drinks were taken for at least 24 h before the study. The examination was performed in a quiet room during the daytime. One-channel electrocardiogram (ECG) measurement was performed on all participants for 30 min in supine position after 5 min rest. During the ECG measurement, subjects were instructed to fully relax, stay awake, breathe regularly and not to speak. The choice of the measurement duration 30 min is a trade-off between acquiring a sufficiently long stationary signal capable for analysis and the duration that the studied subjects could tolerate in certain conditions (Abraham *et al* 1986).

2.3. Measurement of ECG and R–R intervals

As previously described (Chen *et al* 2006), the acquired one-channel analogue ECG signals were converted into digital signals by a 16-bit analogue-to-digital converter with a sampling rate of 500 Hz. The digitized ECG signals were processed off-line. The R waves were first

detected, and then artifacts and ectopic beats were eliminated. If the percentage of elimination was >5%, the ECG signals were discarded. The time intervals between each R–R wave were calculated to obtain a sequence of normal R–R intervals. A total of 2000 beats were used for subsequent analysis. The mean R–R interval and the SDNN were computed from the sequence of normal R–R intervals.

2.4. Correlation dimension analysis of HRV

According to Takens theorem (Takens 1981), we can generate a multidimensional reconstructed state space from a single time series signal to characterize a nonlinear dynamical system. In addition, if the reconstructed state space is generated properly, the behavior of trajectories in this reconstructed state space will have the same geometric and dynamical properties that could characterize the actual trajectories in the full state space for the system. The method of delay embedding was used to reconstruct the multidimensional state space from the original sequence (Takens 1981). This was done by building vectors with components that are separated at multiples of a delay time interval. We first performed state space reconstruction from the sequence of normal R–R intervals,

$$x(i), \qquad i = 1, 2, \ldots, N',$$

to a set of m-dimensional vectors,

$$X_i = [x(i), x(i+\tau), x(i+2\tau), \ldots, x(i+(m-1)\tau)], \qquad i = 1, 2, \ldots, N' - (m-1)\tau$$

where N' is the number of samples, m is the embedding dimension and τ is the delay time, which is the time interval between the samples used to construct the vector X_i. The delay time τ was determined as the earliest time at which the autocorrelation function drops to $1/e$ (e: Euler number) of its initial value (Albano *et al* 1988). The autocorrelation function $A(k)$ is defined as

$$A(k) = \frac{1}{N'-k} \sum_{i=1}^{N'-k} x(i)x(i+k)$$

and it gives information on the time correlations present in the studied signal.

Then, we calculated the correlation sum $C(r)$, which represents the probability of any two arbitrary vector points that separated by a distance less than or equal to r on the trajectories in the reconstructed state space. The correlation sum $C(r)$ was calculated as

$$C(r) = \frac{2}{N(N-1)} \sum_{i=1}^{N} \sum_{j=i+1}^{N} \Theta(r - |X_i - X_j|)$$

where r is the radius, $N(= N' - (m-1)\tau)$ is the number of vector points in the reconstructed state space, X_i and X_j are vector points on the trajectories in the reconstructed state space, $\Theta(s)$ is the Heaviside function defined as

$$\Theta(s) = \begin{cases} 1 & \text{if} \quad s \geqslant 0 \\ 0 & \text{if} \quad s < 0 \end{cases}$$

and $|X_i - X_j|$ is computed as the Euclidean norm.

Finally, the correlation dimension CD is defined as

$$\mathrm{CD} = \lim_{r \to 0} \frac{\ln C(r)}{\ln r}.$$

According to the Grassberger and Procaccia algorithm (Grassberger and Procaccia 1983a, 1983b), CD can be determined by calculating the slope of the straight line that best fits in

the linear scaling region in the plot of $\ln C(r)$ versus $\ln r$. Each embedding dimension m corresponds to an estimated CD. As the embedding dimension m increases, the estimated CD tends to reach a constant saturation value. This constant value is the value of CD for that specific time sequence.

2.5. Surrogate data test

In order to check whether our original R–R interval time sequences are originated from nonlinear dynamical systems, a surrogate data test was performed (Theiler *et al* 1992). Surrogate data sets were generated from the phase randomization of the fast Fourier transform of the original sequences. Next, we tested the hypothesis that there is no difference in CD values between our original data and the surrogate data. If the null hypothesis is rejected, the original sequence is originated from a nonlinear dynamical system. Otherwise, the original sequence favors a random sequence.

2.6. Assays

The laboratory diagnosis of hyperthyroid Graves' disease is mainly established by the high serum thyroid hormone concentrations and the low serum thyrotropin (= thyroid-stimulating hormone (TSH)) concentrations. The normal thyroid gland secretes the thyroid hormones, thyroxine (T4) and triiodothyronine (T3), in response to the TSH, which is one of the anterior pituitary hormones. T4 is the major hormone secreted by the thyroid gland and it is converted in many tissues to the more potent T3. In the blood, both T4 and T3 are bound reversibly to plasma proteins. Only the free form thyroid hormones enter cells and produce biologic effects.

In general, the measurement of the serum or the plasma concentrations of the thyroid hormones consists of the measurement of the total form and the free form thyroid hormones. The free form thyroid hormone, free T4 (FT4) (or free T3 (FT3)), denotes the T4 (or T3) that is not bound with proteins, whereas the total form thyroid hormone, total T4 (or total T3) represents the combination of both the bound and unbound T4 (or T3). Serum total T3, total T4, FT3, FT4 and TSH were measured with a luminescent immunoassay (Vitros assay, Ortho-Clinical Diagnostics, UK).

2.7. Statistical analysis

Data were expressed as means $\pm$ SE. The Mann–Whitney U test was used for all comparisons. Correlations between serum thyroid hormone concentrations and CD were computed by Spearman's correlation coefficient. A P value <0.05 was considered significant. Data were analyzed using SPSS for Windows (SPSS, USA).

3. Results

The hyperthyroid patients were confirmed by high serum thyroid hormone levels (total T3: 8.33 ± 0.46 nmol L^{-1}, normal range 1.49–2.60; total T4: 258.4 ± 9.7 nmol L^{-1}, normal range 71.2–141; FT3: 29.74 ± 1.06 pmol L^{-1}, normal range 4.26–8.10; FT4: 69.1 ± 2.8 pmol L^{-1}, normal range 10.0–28.2) and low serum TSH levels (0.006 ± 0.002 mIU L^{-1}, normal range 0.465–4.68).

The hyperthyroid patient (figure 1(b)) reveals a reduced variation of the amplitudes of the R–R interval sequence compared with the normal control subject (figure 1(a)) in the tachogram. In addition, the intuitive calculations of this variation, the SDNN, show smaller values in the

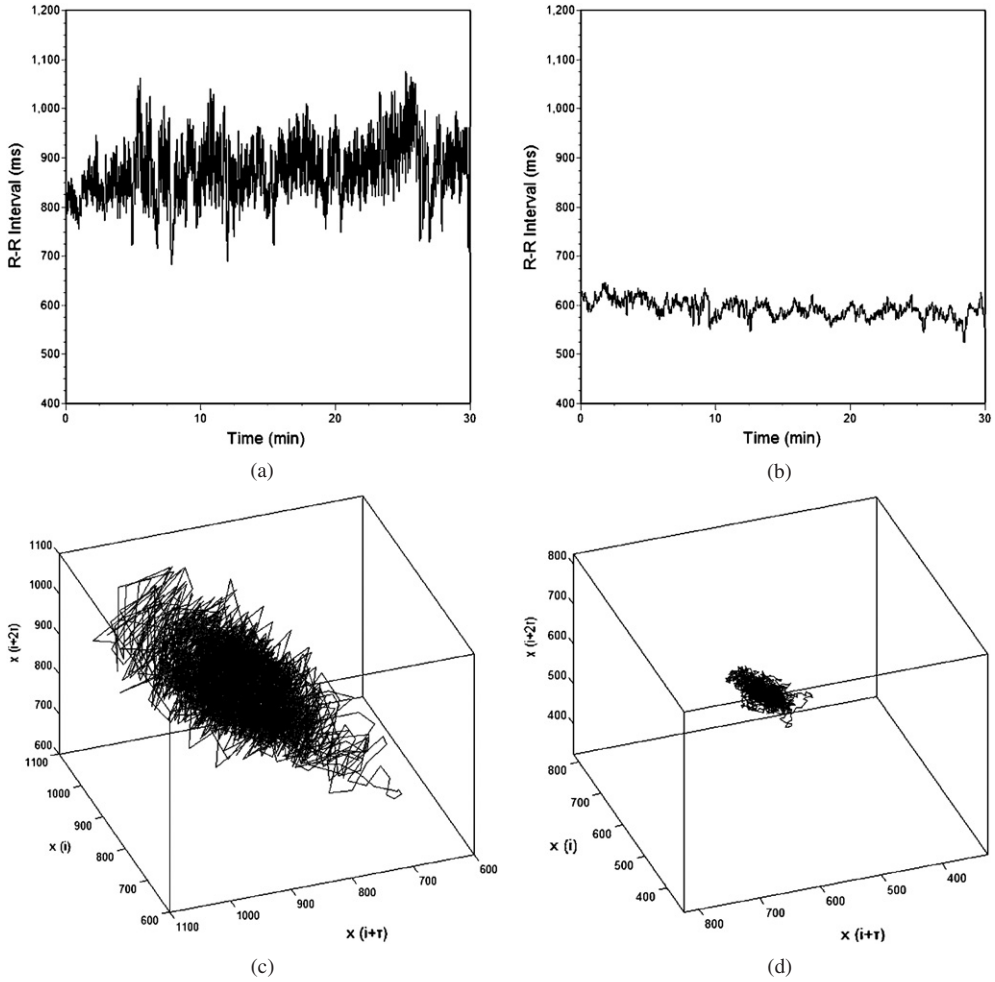

Figure 1. R–R interval tachogram of a normal control subject (a); a hyperthyroid patient (b); the corresponding three-dimensional reconstructed state space plots of the normal control subject (c); and the hyperthyroid patient (d). The unit of all coordinate axes is milliseconds (ms) in the reconstructed state space plots.

hyperthyroid patients compared with the normal control subjects (table 1). Comparing with the normal control subject, the lower value of the averaged R–R interval of the hyperthyroid patient could be visually perceived from the tachogram (figure 1). This implies a faster mean heart rate in the hyperthyroid patients. A significant decrease of the mean R–R interval in the hyperthyroid patients confirms this inspection (table 1).

The three-dimensional reconstructed state space plots were obtained by setting the embedding dimension equals to three. The reconstructed state space plot of the hyperthyroid patient (figure 1(d)) shows a reduced dispersion of vector points compared with that of the normal control subject (figure 1(c)). This indicates a smaller attractor and a less complex structure of the R–R interval system in the hyperthyroid patients.

Figure 2 presents the typical plots of $\ln C(r)$ versus $\ln r$ calculated for various embedding dimension in a normal control subject (figure 2(a)) and a hyperthyroid patient (figure 2(b)). The scaling region is set in the middle third of the vertical range of the plot of $\ln C(r)$ versus

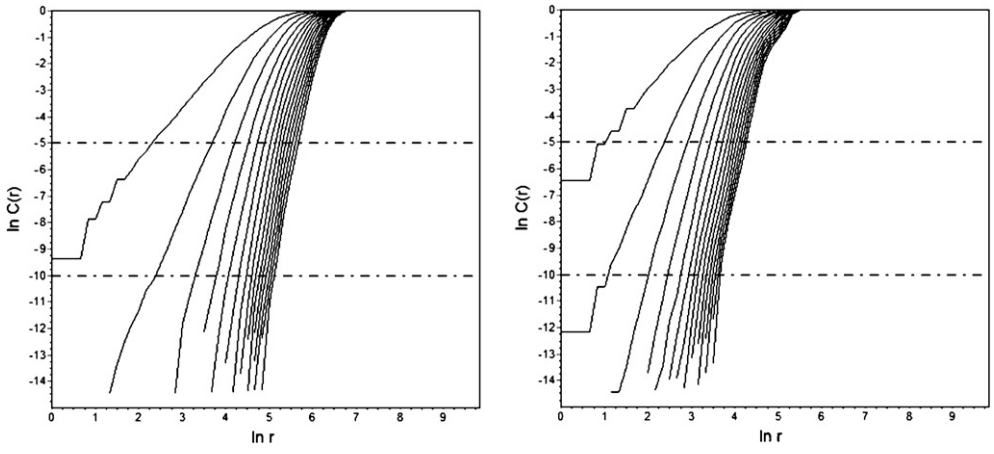

Figure 2. Plots of $\ln C(r)$ versus $\ln r$ with respect to different embedding dimension in a normal control subject (a) and a hyperthyroid patient (b). The scaling region is set in the middle third of the vertical range.

Table 1. Parameters of heart rate variability in hyperthyroid patients and normal control subjects.

	Controls ($n = 33$)	Hyperthyroid ($n = 33$)	P value
RRI (ms)	868 ± 16	616 ± 15	<0.001
SDNN (ms)	54 ± 4	25 ± 2	<0.001
CD	6.42 ± 0.16	5.02 ± 0.11	<0.001

Data are means $\pm$ SE. Differences between means were assessed by the Mann–Whitney U test. RRI = mean R–R interval; SDNN = standard deviation of R–R intervals; CD = correlation dimension.

$\ln r$ (Henry *et al* 2000). The scaling region covers the linear portion of curves in these plots (figure 2). The slope of the scaling region of each curve (corresponding to each embedding dimension) was calculated and the results were plotted against the embedding dimension (figure 3). The saturation value of these slopes was designated as the CD for the specific system. It is evident that the value of CD in the hyperthyroid patient (figure 3(b)) is lower than that of the normal control subject (figure 3(a)). This is further confirmed by a significant decrease in CD of the hyperthyroid patients compared with that of the normal control subjects (hyperthyroid 5.02 ± 0.11 versus control 6.42 ± 0.16, table 1).

A significant difference was noted in CD values between the original data and the surrogate data for both the hyperthyroid patients and the normal controls. Thus, the null hypothesis was rejected. This suggests that our original sequences are originated from nonlinear dynamical systems. There was no correlation between serum thyroid hormone concentrations (total T3, total T4, FT3 and FT4) and CD in the hyperthyroid patients.

4. Discussion and conclusion

Our results revealed that CD values were significantly lower in the hyperthyroid patients compared with the normal control subjects. This suggests that CD could serve as an adequate parameter to distinguish hyperthyroid patients from normal controls.

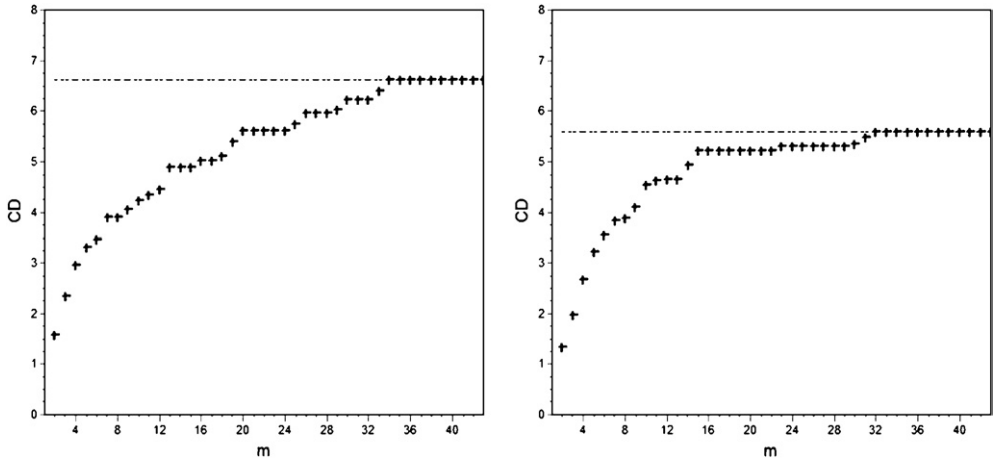

Figure 3. Plots of estimated correlation dimension (CD) versus embedding dimension (m) in a normal control subject (a) (CD = 6.62) and a hyperthyroid patient (b) (CD = 5.60).

CD reflects the characteristics of a nonlinear dynamical system through evaluation of geometric features of its attractor in state space. Moreover, CD quantifies the number of independent variables that are necessary to describe a nonlinear dynamical system. The higher the dimension in a system, the greater the required number of variables and the more complex the signal. Therefore, fractal dimension evaluated by CD from a nonlinear dynamical system has been related to the complexity of the system (Denton *et al* 1990, Goldberger 1996, Lipsitz and Goldberger 1992, Lombardi *et al* 1996, Hoyer *et al* 1997). Our finding that CD was decreased in the hyperthyroid patients compared with the normal controls indicates that the heart rate regulating system is less complex in hyperthyroidism. This decreased system complexity impairs the ability to maintain the cardiovascular integrity in the hyperthyroid patients, and thus, reduces their tolerance to cardiovascular stresses. Furthermore, the intolerance to cardiovascular stresses signifies that the cardiac output reserve could have been reduced in the hyperthyroid cardiovascular system. Because the cardiac output reserve is directly correlated with exercise capacity, the reduced cardiac output reserve in hyperthyroidism could explain why the hyperthyroid patients often complain of low exercise capacity or exercise intolerance. The apparent hyperadrenergic manifestations of the hyperthyroid patients as irritability could also be attributed to their intolerance to cardiovascular stresses.

The linear analysis of HRV suggests hyperthyroidism manifests increased sympathetic and decreased vagal modulation of heart rate. The nonlinear analysis of HRV shows that the heart rate regulating system is characterized by reduced system complexity and intolerance to cardiovascular stresses. Thus, the nonlinear analysis of HRV gives additional knowledge on the heart rate regulating system in hyperthyroidism. However, further studies are needed to elucidate the relationships between CD and autonomic nervous system.

There have been studies using CD analysis of HRV to compare patients with normal controls or to stratify high risk patients within a disease group. Guzzetti *et al* (1996) studied seven recently heart transplanted patients and seven controls of similar age, and found that CD were significantly lower in transplanted subjects than in controls. Lombardi *et al* (1996) investigated a group of 35 male patients after acute myocardial infarction. They showed that

patients with reduced left ventricular ejection fraction had smaller CD values. Nikolopoulos *et al* (2003) studied ten coronary artery disease patients and ten normal control subjects. They disclosed that CD values could distinguish coronary artery disease patients from normal controls. And the coronary artery disease patients were associated with lower CD values. Carvajal *et al* (2005) performed CD analysis of HRV in 55 dilated cardiomyopathy patients and 55 healthy control subjects. They found CD values of dilated cardiomyopathy patients were significantly lower than those of controls. In comparison, Bogaert *et al* (2001) studied ten heart transplant patients and ten age-matched healthy control subjects. They showed that CD cannot be used to make a distinction between heart transplant patients and normal controls.

Most studies showed that CD was decreased in patients and in the poor prognostic groups. Similar results were identified in our study. Our hyperthyroid patients as well as the patients in most previous studies all showed decreased CD values compared with the controls. This signifies that reduced complexity and tolerance to cardiovascular stresses in the diseased subjects in view of the R–R interval system. The reduced complexity and tolerance to cardiovascular stresses in the diseased subjects implies low reactivity to the external stimuli in these subjects. In contrast, the healthy normal controls showing greater values of CD reflect greater complexity and tolerance to cardiovascular stresses in their R–R interval system. Having this greater complexity and tolerance to cardiovascular stresses, the healthy normal subjects are more capable to adapt themselves to the external stimuli or perturbations.

The methods of nonlinear analysis of HRV are still under investigation. More studies are needed to verify these methods and to elucidate the possible physiological significance of these parameters. Should these methods be verified, they could provide valuable indicators for disease diagnosis, risk stratification or even treatment guidance.

In conclusion, hyperthyroid patients and normal controls could be distinguished by CD analysis of HRV. Moreover, the decreased CD in hyperthyroid patients implies reduced system complexity and impaired tolerance to cardiovascular stresses in hyperthyroidism. This finding helps to explain exercise intolerance and irritability manifested by the hyperthyroid patients.

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