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Fractal fluctuations in cardiac time series

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Abstract

Human heart rate, controlled by complex feedback mechanisms, is a vital index of systematic circulation. However, it has been shown that beat-to-beat values of heart rate fluctuate continually over a wide range of time scales. Herein we use the relative dispersion, the ratio of the standard deviation to the mean, to show, by systematically aggregating the data, that the correlation in the beat-to-beat cardiac time series is a modulated inverse power law. This scaling property indicates the existence of long-time memory in the underlying cardiac control process and supports the conclusion that heart rate variability is a temporal fractal. We argue that the cardiac control system has allometric properties that enable it to respond to a dynamical environment through scaling.

Keywords: Relative dispersion; Scaling; Heart rate variability; Modulated inverse power law correlations

1. Introduction

In the physical sciences we are most familiar with statistical phenomena that can be modeled with Gaussian statistics and in the non-equilibrium situation with probability densities whose evolutions are described by Fokker–Planck-like equations [1]. The equivalent dynamical description is in terms of Langevin equations whose deterministic force describes the average evolution of the phenomenon and whose random force is usually assumed to be white noise [2]. The phenomena described by these methods are considered to be rather simple dynamically, in that they have characteristic scales with which to describe them. For example, the mean and variance of time series for physical

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observables are assumed to be finite and may therefore be used to characterize the processes. In complex systems the probability density and/or the correlation function are frequently described by inverse power laws [3], in which case the variance and often the mean diverge; the dynamics of such phenomena may typically be described by stochastic fractional differential equations [4] and the development of the probability densities by fractional diffusion equations [4–6]. One class of solutions to these types of equations are random fractal processes [7]. What is surprising is the ubiquity of phenomena in the physical and life sciences that these random fractal processes describe [8]. In particular, in the interbeat interval fluctuations in the human heart, we find long-term memory embedded in the randomness.

Meesmann et al. [9] demonstrate the self-affine nature of the human heart rate by means of counting. Like the original time series, the number of heart beats in a given time interval scales with the length of time as a power law, a result also obtained by Turcott and Teich [10] using counting statistics. The index for this power law provides the fractal dimension for HRV. Peng et al. [11] employed two distinct measures of heart rate variability (HRV), the statistical distribution of increments in the cardiac beat-to-beat intervals and the spectrum of the same time series. They found that both the statistics and the correlation (spectrum) manifest scaling behavior, the statistics through a Lévy distribution of the fluctuations and the correlations through an inverse power law of the power spectral density. As mentioned by these authors the importance of the Lévy distribution in the description of complex systems like the dynamics of heart rate had been anticipated [1].

The inverse power-law spectrum has been used as an indicator of complexity of physiological phenomena for a number of years. For example, Wagner et al. [12] use the spectrum of blood pressure variability (BPV) to monitor the regulation and control of blood pressure by means of baroreflex mechanisms. Comparing the slope of the spectrum and other indices of complexity, in control and baroceptor denervated conscious dogs, they conclude that denervation of baroreceptor increases the spectral slope and decreases the fractal dimension, indicating a decrease in the complexity of arterial blood pressure control. This result, in fact, supports the hypothesis that an increase in the slope of the spectrum may indicate a deterioration of system control, and therefore, the health of an individual [13,14].

When the probability density has an inverse power-law form, say $(B+t)^{-\alpha}$, there is significant probability that extreme values of the random variable are non-negligible. The mean value associated with this process is

$$\tau \propto \int_0^\infty \frac{t}{(B+t)^\alpha}\,\mathrm{d}t \tag{1}$$

where τ is finite for $\alpha > 1$ and diverges to infinity for $0 < \alpha < 1$. The latter situation corresponds to one form of a fractal random process in which the phenomenon being described cannot be characterized by a finite time scale. The divergence of τ indicates that a large number of time scales contribute to the process with no one of them dominating [8].

There are two kinds of fractal time series, those that are random and those that are not, but both have a fractal dimension. In addition, when the time series is a random fractal it can have two distinct sources of randomness, one being noise and the other being chaos. In the case of noise, the system of interest is coupled to an infinite-dimensional environment, and the influence of the environment on the system is random as is familiar from physical systems [1]. The random fluctuations in this case contain no information about the system, so one is justified in smoothing (filtering) the time series. In the case of chaos, on the other hand, the erratic behavior of the time series is a consequence of deterministic, nonlinear, dynamical interactions among the components of the system [15]. Chaotic motion includes an infinite number of unstable periodic motions. A chaotic system never remains long in any of these unstable motions, but continuously switches from one periodic motion to another, thereby giving the appearance of randomness. Thus, the random fluctuations in the case of chaos contain information about the system and we wish to extract this information from the observed time series, not suppress it. Herein we attempt to determine the source of the fractal behavior observed in cardiac time series, and thereby determine if the existence of such behavior is useful in the characterization of the health and control of the cardiac control system.

A number of investigators have established that a chaotic time series and colored noise, that is, noise with an inverse power-law spectrum, are indistinguishable using various statistical measures. For example, they both have a fractal dimension that can be obtained using a correlation function in an increasing dimensional embedding space [16–18]. Another measure, that of the K_2-entropy, which is a lower bound on the sum of the Lyapunov exponents, was shown [19] to converge to zero for a colored noise process. Therefore, finding a positive largest Lyapunov exponent in a time series, in and of itself, is not sufficient for one to conclude that the dynamical process is chaotic. The problem of distinguishing chaos from noise was partially resolved with the introduction of the surrogate data concept, that is, randomize the phases between data points, thereby destroying the determinism in a chaotic signal, but not influencing colored noise in any substantial way. Thus, if the fractal dimension in the surrogate data is different from that of the original data in a statistically significant way the process has a strong nonlinear component. We find this to be the case in the analysis of the HRV time series in Section 3.

We argue here and elsewhere [20,21] that a random fractal time series in a physiological context is a consequence of a feedback control system that operates over multiple time scales such that there is no fundamental time scale in the control process, thus, a random fractal time series manifests scaling in the distribution function.

In this paper, the time scaling property of HRV is analyzed by using the relative dispersion, the ratio of the standard deviation to the mean, as an indicator of the fractal nature of the time series. One reason for choosing this method over and above others, such as the spectral analysis of Kobayashi and Mushi [22] who were the first to find an inverse power law for an HRV time series, is that it requires little pre-processing of the original data which might, by itself introduce correlations into an otherwise completely random data sequence [21]. Furthermore, the RD method is fairly accurate, even using relatively small data sets [23].

We explicitly demonstrate that HRV is fractal in character using relative dispersion of the systematically aggregated time-series data. The relative dispersion analysis is developed as a measure of scaling in Section 2 using a renormalization group approach. The repeated application of the renormalization group operation, which decimates the underlying temporal structure, captures successively the effects of longer and longer time scales of fluctuations on the largest-scale variations of interest. An explicit reference to fluctuations of a given scale is eliminated by coarse graining the observable. This procedure has been successfully implemented in the study of cerebral blood flow, using trascranial Doppler ultrasonography, showing that the axial blood flow in the middle cerebral artery is a chaotic process [24]. In Section 3 this analysis is applied to the HRV data and the functional form for the relative dispersion is fit to the data and confirms this scaling. The agreement between renormalization group theory and the HRV time-series data is quite good. The renormalization of a biological process indicates that through coarse graining of a particular type, one can determine if the phenomenon has universality and scaling. By universality we mean that the macroscopic properties of the system are independent of the particular microscopic mechanisms present in the phenomenon, which in the present context would be the myriad of physiological subsystems that control HRV. The scaling property is discussed in Section 4 in terms of a cardiac control system having allometric properties.

2. Aggregated relative dispersion and scaling

In observational time series the correlation between adjacent time intervals is greater than that between more distant intervals. The variation, however, often shows "self-similarity upon scaling", for example *the correlation between neighbors in intervals of seconds is the same as correlations between neighbors in intervals of minutes*, even though the unit of time has changed by a factor of 60 between the two comparisons. The fractal dimension captures this kind of inter-relatedness of the data across multiple time scales. Note that this scaling implies strong coupling between widely spaced time intervals, so that in the case of HRV it implies a regulation of HR that is not tied to any rate, but instead allows the cardiovascular control system to access all possible rates with equal facility.

We know from previous studies that a fractal time series has correlations extending over longer time intervals than would ordinarily be expected than say those generated by simple random walks [1,3]. Van Beek et al. [25] show that the correlation between nearest neighbors in a spatially heterogeneous system, which is to say a system whose properties vary with position, was defined by the fractal dimension describing the degree of heterogeneity in a size-independent fashion. This heterogeneity is expressible directly in terms of the correlation coefficient between nearest neighbors, having equal-size regions (independent of the actual size):

$$r_1 = 2^{3-2D} - 1\ . \tag{2}$$

In addition to spatially inhomogeneous data, Eq. (2) is also applicable to fractal random time series, where D is the fractal dimension in either case. If there is no correlation in the time series, $r_1 = 0$, the local irregularities are completely random and the fractal dimension is $D = 1.5$. If, on the other hand, the nearest neighbors are perfectly correlated, $r_1 = 1$, the irregularities are uniform at all times and the fractal dimension is $D = 1.0$. Most time series have fractal dimensions that fall somewhere between these two extremes of uncorrelated Brownian motion ($D = 1.5$) and complete regularity ($D = 1.0$).

Herein we analyze the heterogeneity or variational properties of the beat-to-beat (RR) intervals by determining how the variance depends on the size of the time units used to measure these intervals. We focus our attention on a scale-independent method of assessing temporal heterogeneity called the relative dispersion (RD_y) of the time series (Y_j). This measure is given by the ratio of the standard deviation, SD_y, to the mean, $\overline{Y}$,

$$\mathrm{RD}_y = \frac{\mathrm{SD}_y}{\overline{Y}}\ . \tag{3}$$

The relative dispersion is related to the index of dispersion, also known as the Fano factor, which is the ratio of the variance to the mean rather than the standard deviation to the mean. The Fano factor was introduced by Fano in his investigation of cosmic rays to quantify the degree of clustering of bursts of ionization produced by cosmic rays [26]. A point of reference for this measure is given by a Poisson process, since a Poisson process has the same value for the mean and variance, its Fano factor is unity. A Fano factor greater than one can then be interpreted as a process that clusters and a Fano factor less than one describes a process that is anti-clustering or regular.

Scaling relationships can often be used to describe the apparent heterogeneity over some fairly large range of scales. This analysis allows for a concise description of the variability of the measured property. The general relationship was observed in an empirical physiological context by Bassinghthwaighte [27] to exhibit a linear relationship between the logarithm of the variance, or the relative dispersion, and the logarithm of the size of the observed unit. The idea is to form groups from a data set consisting of m consecutive data points. Firstly, the aggregate of each group is determined and then the relative dispersion of these aggregates are calculated. We then determine how each group and the relative dispersion of these groups change as the aggregates are enlarged to contain more and more data points.

We denote the time of occurrence of the R peaks in the analog ECG signal by t_j, $j = 1, 2, \ldots, N$ and by $\{t_j\}$ the set of times in a cardiac time series. Turcott and Teich [10] treat the set $\{t_j\}$ as a point process and discuss the statistics of the counts in a given interval of time. They calculate the fractal dimension of the underlying attractor generating this sequence to be slightly greater than three. Herein, instead of this point process, we consider the inter-beat intervals in the cardiac time series to be $Y_j = t_{j+1} - t_j$, a typical example of which is shown in Fig. 1. The correlation of the

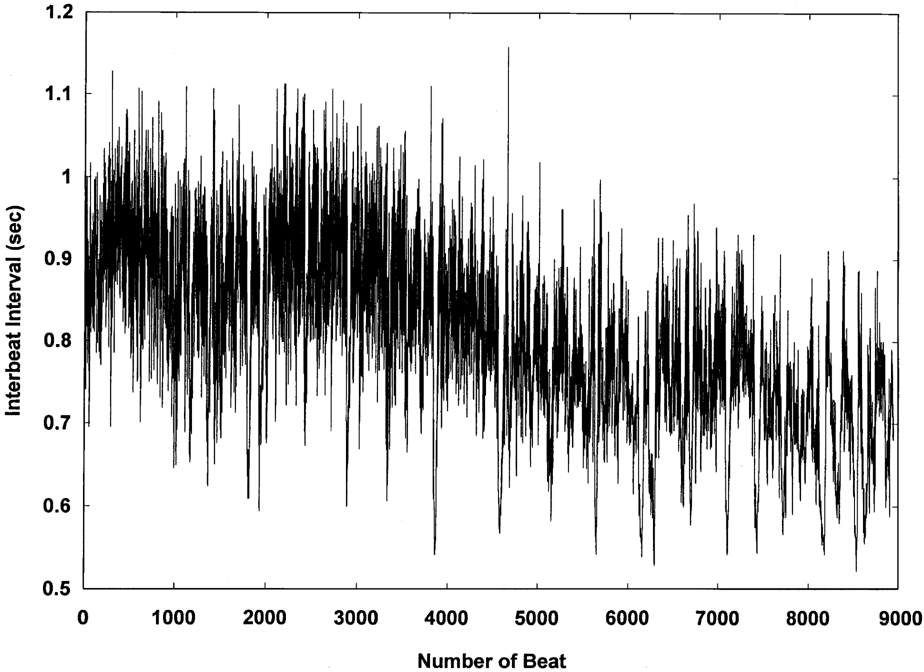

Fig. 1. The sizes of the interbeat intervals are plotted as a function of the beat number for 2 h of data, using a typical member of the group of six subjects.

interbeat data at a given time with other interbeat data in time domains beyond their immediate neighborhood is found by grouping heartbeat intervals into groups of twos, then into groups of threes, then into groups of fours and so on. At each grouping we calculate the relative dispersion. In this way the fractal dimension that is independent of the degree of coarse graining can be determined. Let us examine how the correlation coefficient changes as a function of the number of data elements we aggregate. To see this we coarse-grain n adjacent intervals of the data to obtain the average expressed in terms of

$$Y_j^{(n)} = Y_{nj} + Y_{nj-1} + Y_{nj-2} + \cdots + Y_{nj-n+1} \tag{4}$$

and the average of the aggregated data is

$$\overline{Y}^{(n)} = \frac{n}{N} \sum_{j=1}^{[N/n]} Y_j^{(n)} = \frac{n}{N} \sum_{j=1}^{[N/n]} (Y_{nj} + Y_{nj-1} + Y_{nj-2} + \cdots + Y_{nj-n+1}) = n\overline{Y} \tag{5}$$

where $[\cdot]$ indicates the nearest integer value to the number in the brackets. The relative dispersion for the aggregation of n adjacent data points is then given by

$$\mathrm{RD}_y(n) = \frac{\sqrt{\mathrm{Var}\, Y^{(n)}}}{\overline{Y}^{(n)}} = \frac{\mathrm{SD}_y(n)}{n\overline{Y}} \tag{6}$$

where we have used Eq. (5). The variance of these coarse-grained time series, under the assumption that the interbeat time intervals scales, is given by

$$\mathrm{Var}\, Y^{(n)} = n^{2H}\, \mathrm{Var}\, Y^{(1)} \tag{7}$$

which when inserted into Eq. (6) yields

$$\mathrm{RD}_y(n) = \mathrm{RD}_y(1) n^{H-1} \tag{8}$$

where $\mathrm{RD}_y(1)$ is the unaggregated relative dispersion. Note that Eq. (8), like Eq. (7), has the form of a scaling relation. Let us consider the consequences of such scaling relations.

Consider the two independent parameters a and b, and a function $Z(r)$ such that we can write the renormalization group scaling relation

$$Z(br) = aZ(r)\,. \tag{9}$$

Note that if $a = b^{1-H}$ and $b = 1/r$, then Eq. (9) is exactly of the form (8). Scaling relations of the form (9) have solutions in the same way that differential equations have solutions, which is to say that the dynamics of the phenomenon are determined by finding the general form of the function that obeys the scaling relation (9). One technique for solving such scaling equations is by guessing the solution and determining if the assumed form of the solution satisfies the equation. In this spirit we assume the solution

$$Z(r) = A(r) r^{\mu} \tag{10}$$

which when substituted into Eq. (9) separates into the two equations

$$b^{\mu} = a \quad \text{and} \quad A(br) = A(r)\,. \tag{11}$$

The first of these relations yields the familiar power-law index $\mu = \log a/\log b$. The second of these equations indicates that the function $A(r)$ is periodic in the logarithm of the aggregation size, r, with a period given by $\log b$. Thus, we conclude that the relative dispersion for a fractal random process (FRP) should have the functional form

$$\mathrm{RD}_y(r) = \frac{A(r)}{r^{D-1}} \tag{12}$$

where $D = E + 1 - H$. where D is the fractal dimension for the time series, E is the Euclidean dimension, and $E = 1$ for a time series. Further, since the equation for the relative dispersion, Eq. (8), is of the renormalization group form, the underlying process is an FRP. Note that we determined a general form for the coefficient, $A(r)$, in terms of a Fourier series expansion [8]. However, a more interesting form of the modulation function is the empirical relation

$$A(r) = \exp[\alpha + \lambda \cos(\gamma \log r)] \tag{13}$$

which is a periodic function in the logarithm of r with period $\exp[2\pi/\gamma]$, the latter being equivalent to $\log b$ in Eq. (11), that is, the fractal dimension is given by $D = 2 - H = 1 - \log a/\log b$, α fixes the overall amplitude and λ determines the amplitude of the harmonic modulation.

3. Methods and results

3.1. Subjects

Six healthy subjects (5 men and 1 woman) with a mean age of 29 $\pm$ 8 yr, height of 177 $\pm$ 7 cm, and weight of 76 $\pm$ 14 kg , voluntarily participated in the study. All were non-smokers and were free of known cardiovascular, pulmonary, and cerebrovascular disorders. Each subject was informed of the experimental procedures and signed a written consent form approved by the Institutional Review Boards of The University of Texas Southwestern Medical Center and Presbyterian Hospital of Dallas.

3.2. Procedures and measurements

All experiments were performed at least 2 h of postprandial, and more than 24 h after the last caffeinated beverage or alcohol, in a quiet, environmentally controlled laboratory, with an ambient temperature of 25°C. After at least 30 min of supine rest, analog electrocardiogram (ECG Monitor, Hewlett Packard) was monitored continuously for 2 h during spontaneous respiration. Arterial pressure was also measured continuously in the finger using photoplethysmography (Finapres, Ohmeda). Beat-to-beat HR was obtained with peak detection of R waves using a voltage trigger circuit (Cardiotachometer, Quonton Instrument) and then sampled at 100 Hz and converted into RR interval series for off-line RD analysis. During the 2 h of data recordings, each subject was quiet and awake. Therefore, one unique feature of this study is that we obtain a relatively long data set of HR recordings without external perturbations, and are therefore able to explore intrinsic nonlinear properties of cardiovascular regulation under stationary conditions, should they exist.

We emphasize that most previous studies attempting to demonstrate an inverse power-law spectrum for HRV have used a 24 h Holter recording to obtain data points over sufficiently long time periods or decades of frequency, see for example Refs. [11,28]. However, the physiological state of the subjects is rarely controlled and large amounts of noise (uncontrolled environmental influences) are injected into the time series by talking, eating, physical activity, arousal, etc., that affect heart rate independently of any fundamental control system. We would, therefore, interpret the fractal character, reported in these studies, as being the result of the internal dynamics and the remainder being a consequence of the coupling of the cardiac control system to the environment. In contrast, the data discussed herein are obtained over a prolonged time period under carefully controlled conditions and thus may be uniquely able to assist us in discriminating between chaos and noise in the HRV time series.

3.3. Data analysis

The renormalization group model solution (12) is fitted to the RR interval time series using aggregated relative dispersion. The parameter values are determined from

Table 1
Fitting parameters for the modulated inverse power-law form of the aggregated relative dispersion using HRV data

	α	λ	γ	D
	−3.66	−0.043	0.898	1.09
	−3.34	−0.163	0.628	1.23
	−2.83	0.024	1.309	1.06
	−3.92	−0.178	0.449	1.06
	−3.83	−0.016	0.898	1.19
	−3.92	−0.013	0.967	1.14
AVG	−3.58	−0.065	0.858	1.13
STD	0.43	0.085	0.296	0.07

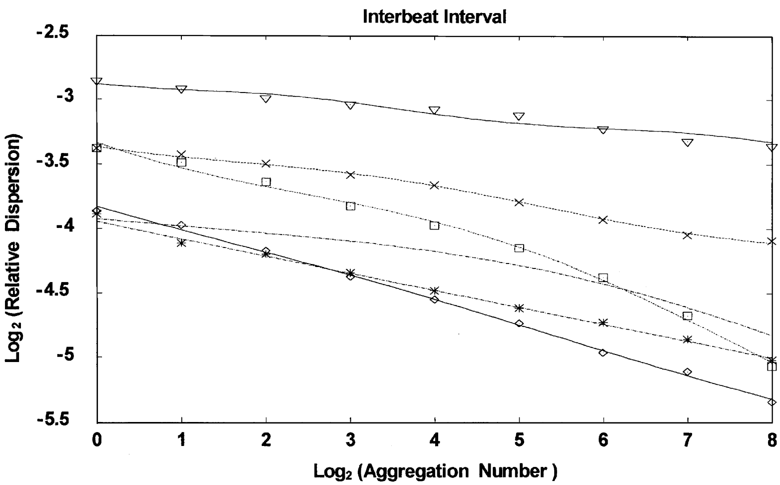

Fig. 2. The logarithm base-two of the relative dispersion is plotted versus the logarithm base-two of the aggregation number for each of the six subjects. Each subject is indicated by a different symbol. The fit to the data is made using the fitting equation (14) and the best-fit parameters are recorded in Table 1.

the fitting equation in which the aggregated relative dispersion is plotted versus the aggregation number on log–log graph paper

$$\log \mathrm{RD}_y(m) = \alpha + (1 - D)\log m + \lambda \cos(\gamma \log m) \tag{14}$$

and are listed in Table 1. We obtain an average fractal dimension for the six subjects of $D=1.13\pm0.07$, a value not inconsistent with those obtained by the previous investigators [11]. In Fig. 2 the relative dispersions given by the data and the fits to these relative dispersions for the six subjects are depicted on log–log graph paper. It is apparent that the dominant behavior is inverse power law, but that behavior is harmonically modulated. The strength of the modulation seems rather weak and changes from person to person as does the fractal dimension. The significance of these two aspects of the scaling remains to be determined.

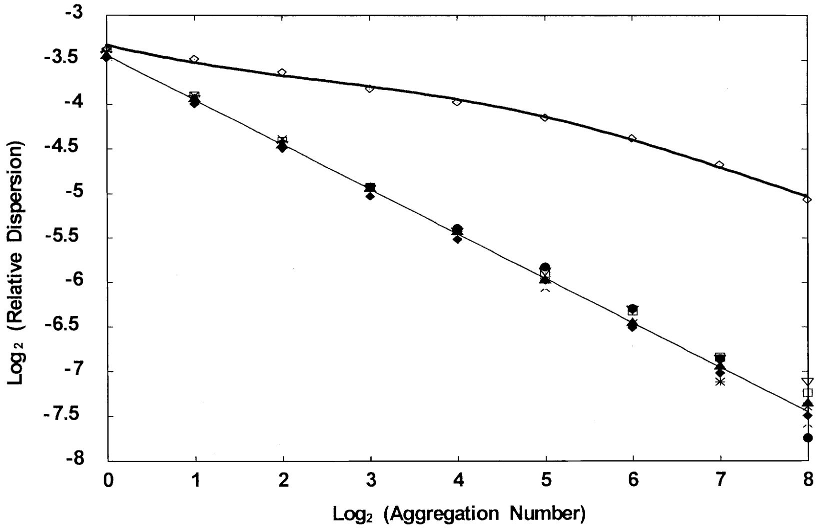

Fig. 3. The logarithm base-two of the relative dispersion is plotted versus the logarithm base-two of the aggregation number for one of the subjects and is depicted by the upper curve which has a fractal dimension of $D = 1.14$. The lower curve depicts the same processing for 10 realizations of a surrogate set constructed from the data generating the upper curve. The slope of the lower curve is $D = 1.50 \pm 0.02$.

To determine if the modulated inverse power law is a consequence of noise or of chaos we implement the surrogate data technique [29] of shuffling the time-series data points to random positions in the sequence for each of the subjects. This procedure neither adds nor removes data points so the statistics of the data set remains unchanged, however, the correlation properties can change markedly. Using ten realizations of the surrogate data for each of the subjects we find that the average values of the λ and γ parameters are zero for each of the subjects. The two remaining parameters for the fitting equation (14) are determined for each of the subjects separately. We find that the intercepts, α, are virtually unchanged, and the fractal dimensions all cluster around $D = 1.5$, that is, 1.50 ± 0.02. The nearest-neighbor autocorrelation coefficient, given by Eq. (2), allows us to interpret the fractal dimension in terms of the correlational properties of the HRV time series. The fractal dimension $D = 1.5$ implies $r_1 = 0$, so there would be no temporal correlations in surrogate data sets for this fractal dimension. This is equivalent to Brownian motion. On the other hand, using the average fractal dimension along with its errors, we find $r_1 = 0.67 \pm 0.047$, for the HRV data, indicating a relatively strong correlation between adjacent RR variations.

In Fig. 3 the relative dispersion data points for a typical one of the six subjects is shown along with the fit using Eq. (14). That fit is compared with the average fit over an ensemble of 10 realizations of the corresponding surrogate time series. The visual difference between the two data sets is striking. The question then arises as to whether the difference between these two fits is statistically significant. We use the fractal dimension as an indicator of the dynamical properties of the HRV time series and determine the level of statistical significance using a t-test:

$$S = \frac{|D - D_{av}|}{SD} \tag{15}$$

where D_{av} is the average fractal dimension for the surrogate ensemble and SD is the standard deviation in the fractal dimensions for that ensemble. The probability of observing a significance S or larger if the random process is linear, additive and uncorrelated is $p = \mathrm{erf}\, c[S/\sqrt{2}]$. Thus, in comparing the fractal dimension of each of the experimental time series with that of the average of the corresponding surrogate ensembles, we require a significance level greater than 0.01. This level of significance is achieved with 10 realizations in each surrogate ensemble with $S > 2.26$. The significance level is determined to be greater than this value in each of the six time series and therefore we observe that the HRV time series for healthy individuals is a random fractal process.

It is obvious from Fig. 3 that in addition to the change in slopes, the fractal dimensions, between the relative dispersions, using the original and the surrogate time-series data, there is also a loss of harmonic modulation. This loss of modulation in the relative dispersion is a further indication that the long-time correlation observed in the original data is a consequence of the underlying dynamics of the phenomenon and that the HRV time series is a temporal fractal.

4. Discussion

The specific mechanisms underlying HRV are not always clear. However, it has been known that heart rate is regulated under a complex feedback control system. Data suggest that this control system at least has the following features. First, it is nonlinear. This property not only manifests as nonlinear interactions between parasympathetic and sympathetic nerve activity which directly controls beat-to-beat changes in heart rate, but also appears in the central nervous system (CNS) which determines the output level of autonomic nerve activity [30]. Second, the system has multiple input signals orginating from sensors located in different parts of the system to monitoring changes in blood pressure, HR and tissue oxygenation. These input signals are converted into and interact with each other at the cardiovascular center in the CNS. Third, the cardiovascular system is a closed feedback and feedforward control system [28]. We hypothesized that the observed HRV time series generated from nonlinear dynamical properties of the cardiovascular system may be chaotic [13,14] in nature.

There are at least five functional roles that chaotic variations, the generic solutions to a nonlinear dynamical system of equations, might play in biological systems, such as HRV: (1) search; (2) defense; (3) maintenance; (4) cross-level effects and (5) dissipation of disturbance [31].

In the first function, that of search, chaotic HRV may act to enhance exploratory activity of the cardiovascular system, that is, heart rate dancing among widely separated values to anticipate possible changes in stress. In the second function, that of defense, the diversity of HR may be helpful to avoid being ensnared in a situation where the heartbeat becomes pathologically regular, and therefore cannot adjust to a changing environment. The maintenance of the heartbeat by chaos arises from the fact that a complex system whose individual elements act more independently are more adaptable than one in which the separate elements move in lock-step. The fourth function, that of cross-level effects, has to do with effects that scale from the shortest to the longest times. This function recognizes that short-term changes in the cardiac control process can have significantly long-term effects. Dissipation of disturbances is a fifth possible function. If the erratic behavior of HRV time series is produced by a strange attractor, on which all trajectories are functionally equivalent, the sensitivity to the initial conditions is the most effective mechanism for dissipating disturbances. Dissipation occurs because the disturbance is so soon mixed with motions that could have been generated by other initial conditions and are therefore consistent with cardiac dynamics.

Chaotic variations in HR imply fractal characteristics of HRV as revealed in the present study. Furthermore, the long-term correlation or memory observed in HRV time series indicates that although different regulatory mechanisms may act independently on different time scales, their effects on dynamical changes in HR may be tied together through scaling. Thus, impairment of one individual component of HR regulation may influence other regulatory mechanisms via interdependence.

The interdependence, organization and concinnity of physiological processes have traditionally been expressed in biology through the principle of allometry. An allometric control system achieves its purpose through scaling, enabling a complex system such as the regulation of HR to be adaptive and accomplish concinnity of the many interacting subsystems. The basic notion is to take part of the system's output and feed it back into the input, thus making the system self-regulating by minimizing the difference between the input and the sampled output. Complex systems such as regulation of HR, that involve the elaborate interaction of multiple sensor systems, have more intricate feedback arrangements. In particular, since each sensor responds to its own characteristic set of frequencies, the feedback control must carry signals appropriate to each of the interacting subsystems. The coordination of the individual responses of the separate subsystems is manifest in the scaling of the time series in the output and the separate subsystems select that aspect of the feedback to which they are the most sensitive. In this way allometric properties of the cardiovascular control system not only regulate HR, but also adapt to changing environmental conditions.

A corollary to the hypothesis that cardiac dynamics are chaotic and therefore HRV time series are scaling and fractal, is that a variety of disease states that alter autonomic function may lead to a loss of physiologic complexity and, therefore, to greater, not less regularity. Decrease in HRV has been described in numerous settings, including multiple sclerosis [32], fetal distress [33], bed-rest deconditioning [34,35] and in certain patients at risk for sudden cardiac death [36]. Presumably, the more severe pathologies will be associated with the greatest loss of spectral power, analogous to that prelude with the most serious arrhythmias, which begin to resemble "sine-wave" patterns. Such spectral narrowing has been referred to as a loss of spectral reserve

[37,38]. Another example of the loss of spectral reserve is presbycusis. With aging, the frequency response of the auditory system typically narrows, with a selective impairment in high-frequency hearing. These and other such findings were anticipated by the West-Goldberger hypothesis that a decrease in healthy variability of a physiological system is manifest in a decreasing fractal dimension [13,14]. Normal HRV depends on the integrity of autonomic regulation, and the stability of cardiovascular control [39]. On the other hand, loss of HRV may indiate impairment of autonomic function and instability of cardiovascular control system. It has been shown that the absence of HRV after an acute myocardial infarction is a risk factor for the development of significant morbidity including arrhythmia, and death [40,41]. Futhermore, HRV is known to be diminished in patients with heart failure [42]. Thus, reliable universal measures of HRV are very important, but in addition a testable theory of the cause of HRV may be potentially more important.

In conclusion, by systematically aggregating the HRV time series, we documented a linear relationship between $\log \mathrm{RD}_y$ and $\log m$ associated with different degrees of harmonic modulation. These data strongly support our hypothesis that HRV time series are temporally fractal, which might be generated by a low-dimensional nonlinear dynamical system via interactions of multiple regulatory mechanisms in the cardiovascular systems. Furthermore, these data suggest that different regulatory mechanisms of the cardiovascular system may be tied together via allometric properties. Therefore, changes in one individual component of the control system may affect other regulatory mechanisms.

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