Long-Range Anticorrelations and Non-Gaussian Behavior of the Heartbeat

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We find that the successive increments in the cardiac beat-to-beat intervals of healthy subjects display scale-invariant, long-range anticorrelations (up to 10^4 heart beats). Furthermore, we find that the histogram for the heartbeat intervals increments is well described by a Lévy stable distribution. For a group of subjects with severe heart disease, we find that the distribution is unchanged, but the long-range correlations vanish. Therefore, the different scaling behavior in health and disease must relate to the underlying dynamics of the heartbeat.

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Scale-invariant properties in biological systems have received much attention recently [1,2]. The absence of characteristic length (or time) scales may confer important biological advantages, related to adaptability of response [2]. In this Letter, we study scale-invariant properties of the human heartbeat time series, the output of an integrative control system. Traditionally, clinicians describe the normal electrical activity of the heart as "regular sinus rhythm." However, cardiac interbeat intervals fluctuate in a complex, apparently erratic manner in healthy subjects even at rest. Analysis of heart rate variability has focused primarily on short time oscillations associated with breathing (0.15–0.40 Hz) and blood pressure control ($\sim$ 0.1 Hz) [3]. Fourier analysis of longer heart rate data sets from healthy individuals typically reveals a $1/f$-like spectrum for frequencies < 0.1 Hz [4–6]. However, the very long-time correlation properties of physiologic heart rate time series and alterations of these correlations in diseased conditions remain uncharted.

Our analysis is based on the digitized electrocardiograms of beat-to-beat heart rate fluctuations over very long time intervals (up to 24 h $\approx 10^5$ beats) recorded with an ambulatory monitor. The time series obtained by plotting the sequential intervals between beat n and beat $n+1$, denoted by $B(n)$, typically reveals a complex type of variability. The mechanism underlying such fluctuations is related to competing neuroautonomic inputs. Parasympathetic (vagal) stimulation decreases the firing rate of pacemaker cells in the heart's sinus node; sympathetic stimulation has the opposite effect. The nonlinear interaction (competition) between these two branches of the involuntary nervous system is the postulated mechanism for much of the erratic heart rate variability recorded in healthy subjects [2], although nonautonomic factors may also be important.

To study these dynamics over large time scales, we pass the time series through a digital filter that removes fluctuations of frequencies > 0.005 beat^{-1}, and plot the result, denoted by $B_L(n)$, in Fig. 1. We observe a more complex pattern of fluctuations for a representative healthy adult [Fig. 1(a)] compared to the "smoother" pattern of interbeat intervals for a subject with severe heart disease [Fig. 1(b)]. These heartbeat time series produce a contour reminiscent of the irregular landscapes that have been widely studied in physical systems.

To quantitatively characterize such a "landscape," we introduce a mean fluctuation function $F(n)$, defined as

$$F(n) \equiv \overline{|B_L(n'+n) - B_L(n')|}, \tag{1}$$

where the bar denotes an average over all values of n'. Operationally, this is equivalent to (i) taking a set of calipers set for a fixed distance n, (ii) moving the beginning point sequentially from $n' = 1$ to $n' = 2$, etc., and (iii) calculating the quantity $|B_L(n'+n) - B_L(n')|$ for each value of n', and (iv) averaging all of the calculated quantities to obtain $F(n)$ [7]. Since $F(n)$ measures the average difference between two interbeat intervals separated by a time lag n, $F(n)$ quantifies the magnitude of the fluctuation over different time scales n.

Figure 1(c) is a log-log plot of $F(n)$ vs n for the data in Figs. 1(a) and 1(b). This plot is approximately linear over a broad physiologically relevant time scale (200–4000 beats) implying that

$$F(n) \sim n^{\alpha}. \tag{2}$$

We find that the scaling exponent α is markedly different for the healthy and diseased states: For the healthy heartbeat data, α is close to 0, while α is close to 0.5 for the diseased case. It is interesting to note that $\alpha = 0.5$ corresponds to the well-studied *random walk* (Brownian motion), so the low-frequency heartbeat fluctuations for the diseased state can be interpreted as a stochastic process, in which case the interbeat increments $I(n) \equiv B(n+1) - B(n)$ [8] are uncorrelated for $n > 200$.

One immediate question is whether the marked differences in scaling properties shown in Figs. 1(a) and 1(b) are simply related to different statistical properties of

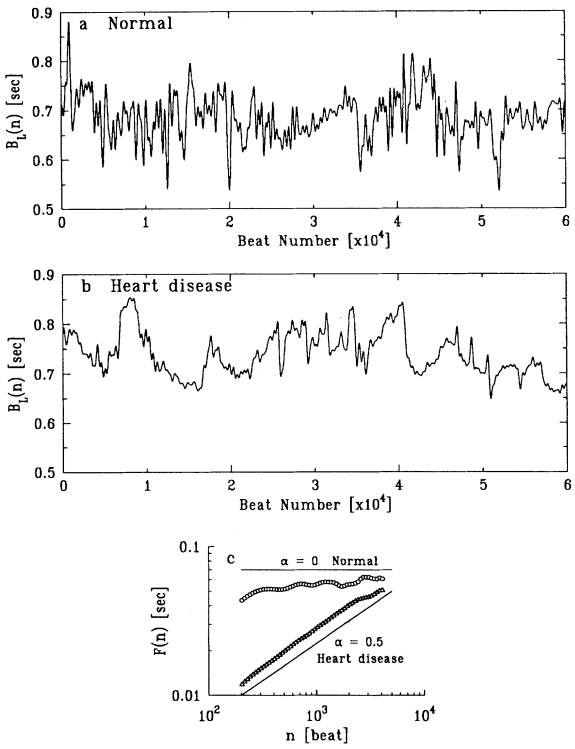

FIG. 1. The interbeat interval $B_L(n)$ after low-pass filtering for (a) a healthy subject and (b) a patient with severe cardiac disease (dilated cardiomyopathy). The healthy heartbeat time series shows more complex fluctuations compared to the diseased heart rate fluctuation pattern that is close to random walk ("Brownian") noise. (c) Log-log plot of $F(n)$ vs n. The circles represent $F(n)$ calculated from data in (a) and the triangles from data in (b). The two best-fit lines have slope $\alpha = 0.07$ and $\alpha = 0.49$ (fit from 200 to 4000 beats). The two lines with slopes $\alpha = 0$ and $\alpha = 0.5$ correspond to "$1/f$ noise" and "Brownian noise," respectively. We observe that $F(n)$ saturates for large n (of the order of 5000 beats), because the heartbeat intervals are subjected to physiological constraints that cannot be arbitrarily large or small. The low-pass filter removes all Fourier components for $f \geq f_c$. The results shown here correspond to $f_c = 0.005$ beat^{-1}, but similar findings are obtained for other choices of $f_c \leq 0.005$. This cutoff frequency f_c is selected to remove components of heart rate variability associated with physiologic respiration or pathologic Cheyne-Stokes breathing as well as oscillations associated with baroreflex activation (Mayer waves).

$I(n)$ for the normal and diseased cases. We find that $I(n)$ for the two time series in Figs. 1(a) and 1(b) have virtually identical histograms, and can be well described by a Lévy stable distribution (see Fig. 2):

$$P(I,\psi,\gamma) = \frac{1}{\pi}\int_0^\infty \exp(-\gamma q^\psi)\cos(qI)dq, \qquad (3)$$

with $\psi = 1.7$ and $\gamma > 0$ [9]. Since the histograms of the increments are the same for both normal and diseased

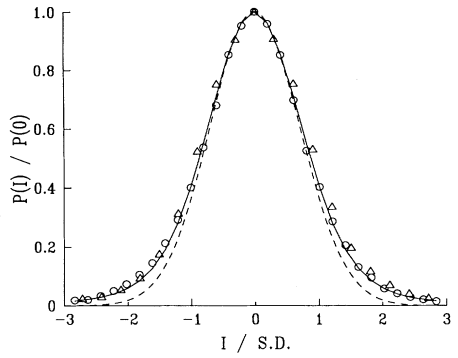

FIG. 2. The histogram of $I(n)$ for the healthy (circles) and diseased (triangles) subjects shown in Fig. 1. $P(I)$ is the probability of finding an interbeat increment in the range $[I - \Delta I/2, I + \Delta I/2]$. To facilitate comparison, we divide the variable I by the standard deviation (S.D.) of the increment data and rescale P by $P(0)$. In Lévy stable distributions, ψ is related to the power law exponent describing the distribution for large values of the variable, while the width of the distribution is characterized by γ. Since we have rescaled I by the width, ψ is the only relevant parameter. Both histograms are indistinguishable and are well fitted by a Lévy stable distribution with $\psi = 1.7$ (solid line). The dashed line is a Gaussian distribution, which is a special case of a Lévy stable distribution with $\psi = 2$. Although the second moment diverges for a Lévy stable distribution, for a finite sample the second moment remains finite. Similar fits were obtained for eight of the ten normal subjects and all ten subjects with heart disease. The slow decay of Lévy stable distributions for large increment values may be of physiological importance and relate to the dynamics of the system.

conditions, *the different scaling patterns in health and disease [Fig. 1(c)] must relate to the ordering of these increments*, i.e., to the correlations between the length of successive increments produced by the underlying dynamics of the heartbeat.

To investigate these dynamical differences, it is helpful to study further the correlation properties of the time series. To this end, we choose to study $I(n)$ because it is the appropriate variable for the aforementioned reason. Since $I(n)$ is stationary, we can apply standard spectral analysis techniques [10]. Figures 3(a) and 3(b) show the power spectra $S_I(f)$, the square of the Fourier transform amplitudes for $I(n)$, derived from the same data sets (without filtering) used in Fig. 1. The fact that the log-log plot of $S_I(f)$ vs f is linear implies

$$S_I(f) \sim f^\beta. \qquad (4)$$

The exponent β is related to α by $\beta = 1 - 2\alpha$ [11]. Furthermore, β can serve as an indicator of the presence and type of correlations: (i) If $\beta = 0$, there is no correlation in the time series $I(n)$ ("white noise"). (ii) If $-1 < \beta < 0$, then $I(n)$ is correlated such that positive values of I are likely to be close (in time) to each other, and the same is true for negative I values. (iii) If $0 < \beta < 1$, then $I(n)$

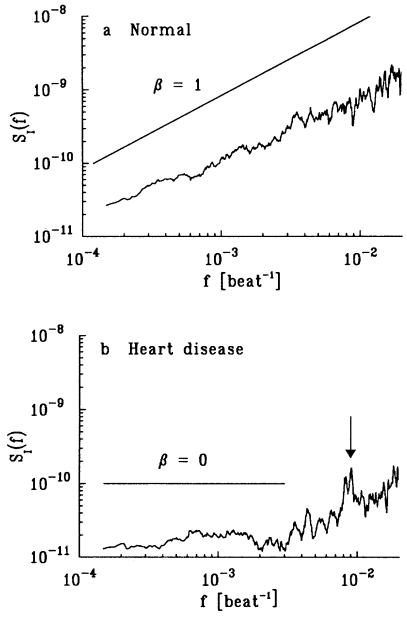

FIG. 3. The power spectrum $S_I(f)$ for the interbeat interval increment sequences over ~ 24 h for the same subjects in Fig. 1. (a) Data from a healthy adult. The best-fit line for the low-frequency region has a slope $\beta = 0.93$. The heart rate spectrum is plotted as a function of "inverse beat number" (beat^{-1}) rather than frequency (time^{-1}) to obviate the need to interpolate data points. The spectral data are smoothed by averaging over fifty values. (b) Data from a patient with severe heart failure. The best-fit line has slope 0.14 for the low-frequency region, $f < f_c = 0.005$ beat^{-1}. The appearance of a pathologic, characteristic time scale is associated with a spectral peak (arrow) at about 10^{-2} beat^{-1} (corresponding to Cheyne-Stokes respiration).

is also correlated; however, the values of I are organized such that positive and negative values are more likely to alternate in time ("anticorrelation") [11].

For the diseased data set, we observe a flat spectrum ($\beta \simeq 0$) in the low-frequency region [Fig. 3(b)] confirming that $I(n)$ are not correlated over long time scales (low frequencies). Therefore, $I(n)$, the first derivative of $B(n)$, can be interpreted as being analogous to the *velocity* of a random walker, which is uncorrelated on long time scales, while $B(n)$—corresponding to the *position* of the random walker—are correlated. However, this correlation is of a trivial nature since it is simply due to the summation of uncorrelated random variables.

In contrast, for the data set from the healthy subject [(Fig. 3(a)], we obtain $\beta \simeq 1$, indicating *nontrivial* long-range correlations in $B(n)$—these correlations are not the consequence of summation over random variables or artifacts of nonstationarity. Furthermore, the anticorrelation properties of $I(n)$ indicated by the positive β value are consistent with a nonlinear feedback system that "kicks" the heart rate away from extremes. This tendency, however, does not only operate on a beat-to-beat basis (local effect) but on a wide range of time scales. To our knowledge, this is the first explicit description of long-range anticorrelations in a fundamental biological variable, namely, the interbeat interval increments.

To test for statistical significance, we analyzed data from two different groups of subjects: ten adults without clinical evidence of heart disease (age range: 32–64 yr, mean 44) and ten adults with severe heart failure (age range 22–63 yr, mean 54). Data from patients with heart failure due to severe left ventricular dysfunction are likely to be particularly informative in analyzing correlations under pathologic conditions since these individuals have abnormalities in both the sympathetic and parasympathetic control mechanisms [5] that regulate beat-to-beat variability. Previous studies have demonstrated marked changes in short-range heart rate dynamics in heart failure compared to healthy function, including the emergence of intermittent relatively low-frequency ($\sim$ 1 cycle/min) heart rate oscillations associated with the well-recognized syndrome of periodic (Cheyne-Stokes) respiration, an abnormal breathing pattern often associated with low cardiac output [5]. This pathologic, characteristic time scale is indicated by a vertical arrow in Fig. 3(b).

For the healthy subjects, we observe the following exponents for the cardiac interbeat interval time series (mean value $\pm$ standard deviation): $\alpha = 0.19 \pm 0.05$ and $\beta = 1.01 \pm 0.16$. For the group of heart failure subjects, we find that $\alpha = 0.41 \pm 0.08$ and $\beta = 0.54 \pm 0.25$, both significantly different from normal [12]. The exponent α is less than 0.5 for the heart failure patients since pathologic dynamics may only transiently operate in the random walk regime or may only approach this extreme state as a limiting case [Fig. 1(b)]. We obtained similar results when we divided the time series into three consecutive subsets (of $\sim$ 8 h each) and repeated the above analysis. Therefore our findings are not simply attributable to different levels of daily activities.

Our finding of nontrivial long-range correlations in healthy heart rate dynamics is consistent with the observation of long-range correlations in other biological systems that do not have a characteristic scale of time or length [1,2,13]. Such behavior may be adaptive for at least two reasons. (i) The long-range correlations serve as an organizing principle for highly complex, nonlinear processes that generate fluctuations on a wide range of time scales. (ii) The lack of a characteristic scale helps prevent excessive *mode locking* that would restrict the functional responsiveness of the organism. Support for these related conjectures is provided by observations from severe diseased states such as heart failure where the breakdown of long-range correlations is often accompanied by the emergence of a dominant frequency mode (e.g., the Cheyne-Stokes frequency). Analogous transitions to highly periodic regimes have been observed in a wide range of other disease states including certain malignancies, sudden cardiac death, epilepsy, and fetal distress syndromes [2].

The complete breakdown of normal long-range corre-

lations in any physiological system could theoretically lead to three possible diseased states: (i) a random walk (Brownian noise), (ii) highly periodic behavior, or (iii) completely uncorrelated behavior (white noise). Cases (i) and (ii) both indicate only "trivial" long-range correlations of the types observed in severe heart failure. Case (iii) may correspond to certain cardiac arrhythmias such as fibrillation. More subtle or intermittent degradation of long-range correlation properties may provide an early warning of incipient pathology. Finally, we note that the long-range correlations present in the healthy heartbeat indicate that the neuroautonomic control mechanism actually drives the system away from a single steady state. Therefore, the classical theory of homeostasis, according to which stable physiological processes seek to maintain "constancy" [14], should be extended to account for this dynamical, far from equilibrium, behavior.

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[8] Unlike the original time series $B(n)$, $I(n)$ is *stationary*, i.e., the average and the variance are independent of the sampling position. We have verified this stationarity property experimentally by measuring the stability of the average and variance in a moving window. Although the nonstationarity property makes no difference for our calculation of $F(n)$, it is important to study a stationary sequence for the correlation analysis. Another advantage of the stationarity property of $I(n)$ is that the comparison of histograms between data from healthy and diseased subjects becomes feasible.

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[12] The relation of $\beta = 1 - 2\alpha$ is valid at the infinite length limit. For time series with finite length, we expect discrepancies between β and α. See C. Peng *et al.*, Phys. Rev. E (to be published), and Nature (London) **356**, 168 (1992), for a detailed analytic and numerical discussion of the finite size effect on long-range correlations. For example, we have simulated artificial correlated sequences (with a given exponent β) of finite length (corresponding to that of the interbeat time series studied here). For $\beta = 1$ we expect $\alpha = 0$, but instead we find $\alpha = 0.12 \pm 0.05$ for the artificial sequences. Similarly, for $\beta = 0.5$ we expect $\alpha = 0.25$ and find $\alpha = 0.28 \pm 0.07$. Another possible reason for the discrepancy is that a heartbeat time series is unlikely to represent "perfect" fractional Brownian motion.

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